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The Role of HGF/c-Met Pathway Signaling in Human Medulloblastoma

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1. Introduction

Medulloblastoma is the most common malignant brain tumor in childhood and represents around 10% of all pediatric cancer deaths. It arises in the cerebellum and originates from aberrant proliferation of neural progenitor cells during development. It has a high tendency to disseminate throughout the central nervous system with as many as 30% of children with metastatic spread at the time of diagnosis. Dissemination is the most important factor associated with poor survival and the leading cause of treatment failure. The current therapies include surgery, radiation and chemotherapy with 5-year survival rates ranging between 50 and 80%. Among long-term survivors, a major concern is the sequelae induced by treatment including endocrinologic, neurocognitive and behavioral dysfunction.

The genetic heterogeneity of medulloblastoma appears to be the basis for differential response to treatment, which leads to the conclusion that current tumor classification systems based solely on histological or clinical criteria are clearly insufficient and limited. Recent studies have identified distinct molecular variants of medulloblastoma that correspond with different clinical presentations, transcriptional profiles, genetic abnormalities and clinical outcomes (Eberhart, 2011; Ellison et al., 2011; Northcott et al., 2010; Pfister et al., 2010). Thus, a better understanding of the molecular biology of this tumor will have significant diagnostic, prognostic and therapeutic value.

Medulloblastoma is associated with dysregulation of the pathways that normally lead to cerebellum development. Over the past few years, different signaling pathways have been shown to play a critical role in medulloblastoma formation and progression. The hepatocyte growth factor (HGF)/c-Met signaling pathway has been implicated in different processes including development and tumorigenesis but only recently has it been demonstrated in medulloblastoma pathogenesis. The receptor tyrosine kinase c-Met is normally activated following engagement with HGF ligand, secreted as a precursor that is proteolytically cleaved in an active form by the serine protease hepatocyte growth factor activator. HGF is a member of the plasminogen-related growth factor family and was originally identified as a growth factor for hepatocytes and as a fibroblast-derived cell motility or scatter factor. The interplay between c-Met and its ligand mediate downstream events that, in the central nervous system, play a critical role in cerebellar granule cell precursors proliferation and survival. Dysregulation of this pathway can promote tumorigenesis through cell migration,

invasion and metastasis, angiogenesis and prevention of apoptosis. Met has been found to be overexpressed in a variety of malignancies where its activation can occur by HGF ligation or through ligand independent mechanisms, including mutations and amplifications.

It was shown that medulloblastoma tumor cell lines and surgical tumor samples express HGF and c-Met. Furthermore, overexpression of c-Met is associated with poor clinical outcome. Treatment of medulloblastoma cell lines with HGF induced tumor cell proliferation, anchorage-independent growth and reduced apoptosis in response to chemotherapy. Recently, *Serine protease inhibitor kunitz-type 2 (SPINT2)*, a tumor suppressor gene silenced by promoter methylation in medulloblastoma, was identified by our group as a key regulator of HGF/c-Met pathway (Kongkham et al., 2008). Several therapeutic strategies aiming to target and limit the signaling cascade of HGF/c-Met were examined with the c-Met inhibitors being the most promising. Targeting the HGF/c-Met pathway, alone or in combination with standard therapies is likely to improve present treatments in Met-dependent malignancies such as medulloblastoma.

In this chapter we examine the role of the HGF/c-Met pathway in normal cerebellar development and in medulloblastoma formation and progression. We also highlight the most recent advances in targeted therapies to the HGF/c-Met axis in cancer.

2. HGF/c-Met pathway signaling

The HGF/c-Met pathway has been associated with normal development, organ regeneration and cancer. Met is a high affinity tyrosine kinase receptor for hepatocyte growth factor (also known as scatter factor, capable of inducing dissociation and motility). Met is generally expressed in epithelial cells and is activated by HGF produced in surrounding mesenchymal cells or released into the circulation.

During embryogenesis HGF/c-Met signaling is necessary for the development of the placenta, liver, kidney and neuronal tissue but also for the directional migration of skeletal muscle cells (Birchmeier & Gherardi, 1998). In adult tissues, this pathway has been implicated in regeneration and wound healing (Chmielowiec et al., 2007; Huh et al., 2004). Therefore, the HGF/c-Met axis is a key player in cell proliferation, survival and migration and, when dysregulated, can give origin to a variety of cancers.

2.1 Structure of HGF and Met

HGF is a multidomain protein similar to plasminogen, a circulating proenzyme that promotes the lysis of fibrin blood clots in its active form as plasmin. HGF is synthesized as a single-chain inactive precursor and it is converted by serine proteases into an active form with two chains (α and β chain) linked by a disulfide bond. HGF consists of six domains: an amino-terminal hairpin loop domain (HL), four kringle domains (K1-K4) and a serine protease homology (SPH) domain which lacks enzymatic activity (**Figure 1**).

Met, the HGF receptor, is a disulfide-linked heterodimer which results from cleavage of a precursor into an extracellular α chain and a transmembrane β chain. The extracellular region of Met is composed of three domains: the Sema domain (homologous to the Sema domain of the semaphorins and plexins) that includes the entire α chain and part of the β chain; the PSI domain (also present in the plexins, semaphorins and integrins); and four IPT domains (immunoglobulin-like also found in plexins and transcriptional factors). The intracellular region of Met consists of three portions: a juxtamembrane sequence that has the

role to downregulate kinase activity upon phosphorylation of Ser975; a catalytic region that activates kinase activity following phosphorylation of Tyr1234 and Tyr1235; and a carboxy-terminal multifunctional docking site that contains two docking tyrosines (Tyr1349 and Tyr1356) essential for downstream signaling (Trusolino et al., 2010).

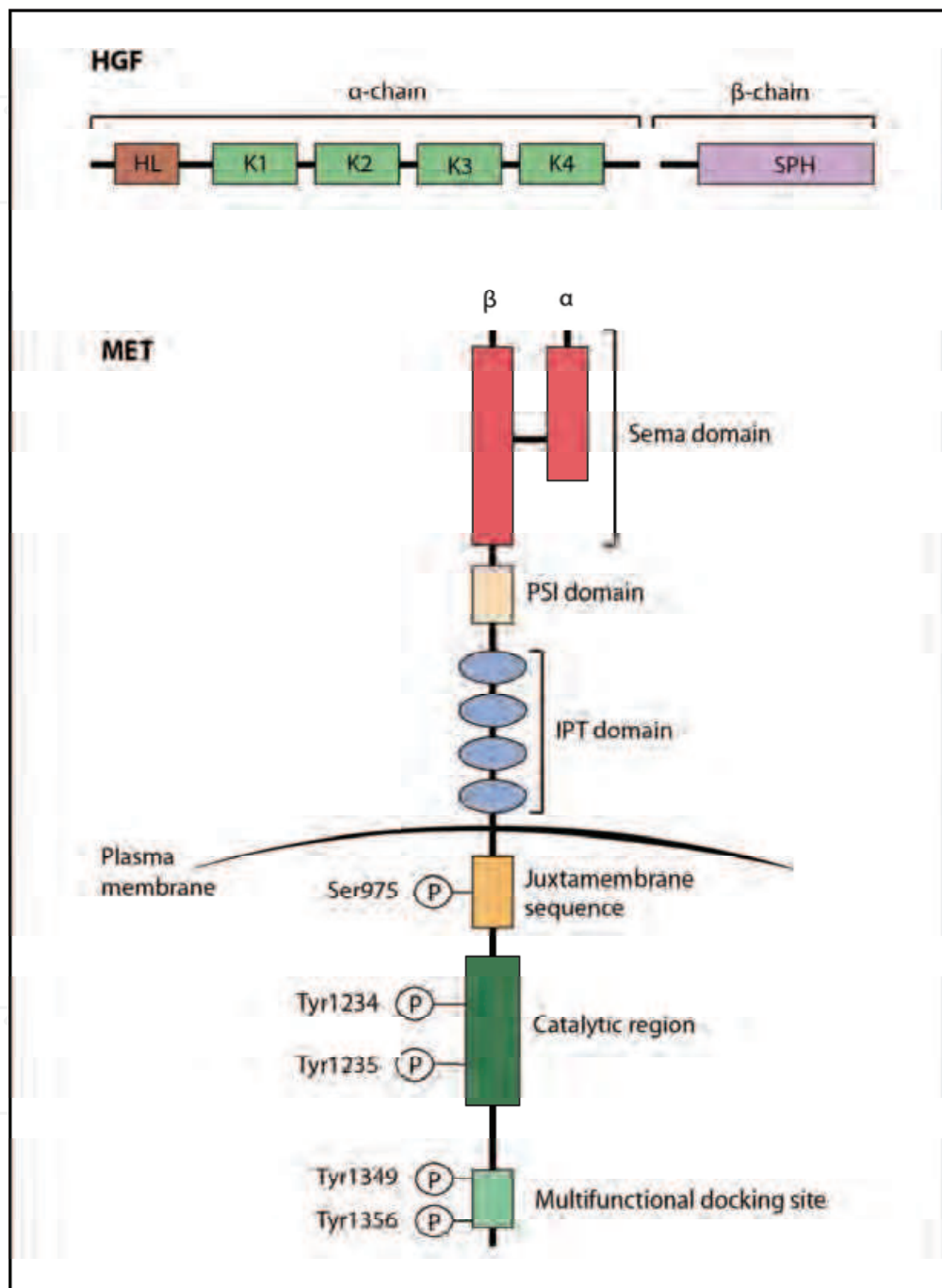


Fig. 1. HGF and Met structures

2.2 Met signal transduction

To activate the Met receptor, the single chain HGF precursor is cleaved into a heterodimeric active form by a protease called HGF activator (HGFA) (Miyazawa et al., 1993). This process

is regulated by a protein family of serine protease inhibitors called SPINT1 and SPINT2 (Kawaguchi et al., 1997; Shimomura et al., 1997). Inhibiting the activation of HGF by HGFA, SPINT1 and -2 limit signaling through the HGF/c-Met pathway.

Following HGF binding, the kinase activity of Met is switched on. This process starts with receptor dimerization and *trans*-phosphorylation of two tyrosine residues in the catalytic region (Tyr1234 and Tyr1235) and is followed by phosphorylation of two additional tyrosines in the carboxy-terminal tail (Tyr1349 and Tyr1356). These tyrosines create docking sites for a variety of adaptor proteins and direct kinase substrates including the growth factor receptor-bound protein 2 (Grb2), Grb2-associated adaptor protein (Gab1), son of sevenless (SOS), SRC homology protein tyrosine phosphatase 3 (Shp2), phosphatidylinositol-3-kinase (PI3K) and signal transducer and activator of transcription 3 (STAT3). This leads to the activation of downstream signaling pathways that include the mitogen-activated protein kinase (MAPK), PI3K/AKT and STAT pathways, which mediate Met-dependent cell proliferation, survival, migration and invasion (**Figure 2**).

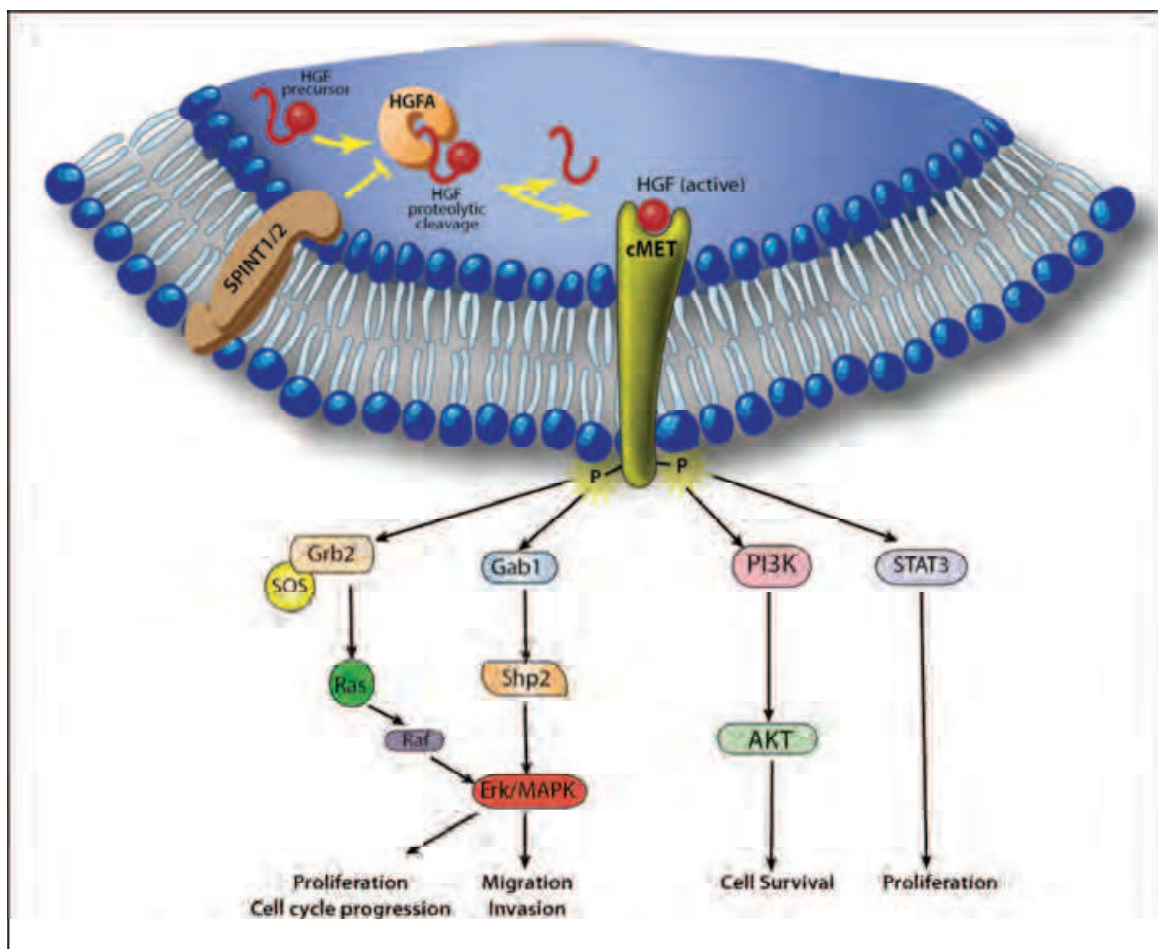


Fig. 2. The HGF/c-Met signaling pathway

The activation of MAPK cascade will sequentially activate different protein kinases whose terminal effectors include extracellular signal-regulated kinases (Erk1 and Erk2), Jun amino-terminal kinases (JNK1, JNK2 and JNK3) and p38. These downstream elements will activate cell cycle regulators leading to cell proliferation and will promote alterations in cytoskeletal functions that control cell migration and invasion. PI3K/AKT activation mediates cell

survival and resistance to apoptosis through inactivation of the pro-apoptotic protein BCL-2 antagonist of cell death (BAD) and degradation of the pro-apoptotic protein p53 (Birchmeier et al., 2003). Upon activation of STAT3 by the Met receptor at the plasma membrane, it translocates to the nucleus to operate as a transcription factor regulating the expression of genes implicated in cell proliferation and differentiation (Y. W. Zhang et al., 2002).

Other molecules that interact with the Met receptor include the epidermal growth factor receptor (EGFR), the $\alpha\beta4$ integrin, the semaphoring receptors of the plexin B family and the variant of the hyaluronan receptor CD44 (that links the extracellular matrix and the intracellular cytoskeleton) (Bertotti et al., 2006; Guo et al., 2008; Orian-Rousseau et al., 2002). This crosstalk of Met with different surface proteins highlights the dynamic environment at the plasma membrane and contributes to Met associated biological responses (Lai et al., 2009).

2.3 Regulation of Met signaling

It has been shown that the signaling network around the tyrosine kinase receptor Met is more complex than the known process of recruiting signaling effectors at the plasma membrane and subsequently stimulating intermediates in the cytosol. In fact, this view has been expanded by the finding that Met signals can also originate from endosomal compartments and by a series of other events.

Upon HGF binding, Met is internalized by clathrin-mediated endocytosis and recruited into peripheral early endosomes. This process is mediated by protein kinase C ϵ (PKC ϵ) that promotes the transfer of active Erk to focal adhesions and, subsequently, the HGF-induced cell migration. From the peripheral endosomes, Met travels along the microtubule network to late perinuclear compartments in a process mediated by PKC α . This juxtannuclear accumulation of Met is a determinant step for activation and nuclear translocation of STAT3 (Kermorgant & Parker, 2005, 2008).

Downregulation of Met signaling involves trafficking and degradation of ligand-activated receptors in the lysosomes. This process is initiated by the association of Met with casitas B-lineage lymphoma (CBL) and endocytic adaptors. Following endocytosis, Met accumulates in multivesicular bodies that later fuse with lysosomes and leads to protein degradation. Met can also undergo sequential proteolytic cleavage at two juxtamembrane sites. The first cleavage occurs in the extracellular domain and is mediated by a disintegrin and metalloprotease (ADAM) originating a 'decoy' fragment that sequesters the ligand and interferes with the receptor's activity. The second cleavage is performed in the intracellular domain, by a γ -secretase and yields a fragment that is destroyed in the proteasome (Hammond et al., 2001)(Figure 3).

3. HGF, Met and cancer

The dysregulation of HGF/c-Met signaling has emerged as a key player in several human malignancies, particularly in invasion and metastasis. Human cell lines overexpressing either HGF and/or Met become tumorigenic and metastatic when implanted into nude mice (Rong et al., 1994). Moreover, transgenic mice expressing the receptor or the ligand develop metastatic tumors (Takayama et al., 1997). On the contrary, downregulation of HGF or Met expression in human tumor xenografts decreases tumor growth (Abounader et al., 2002).

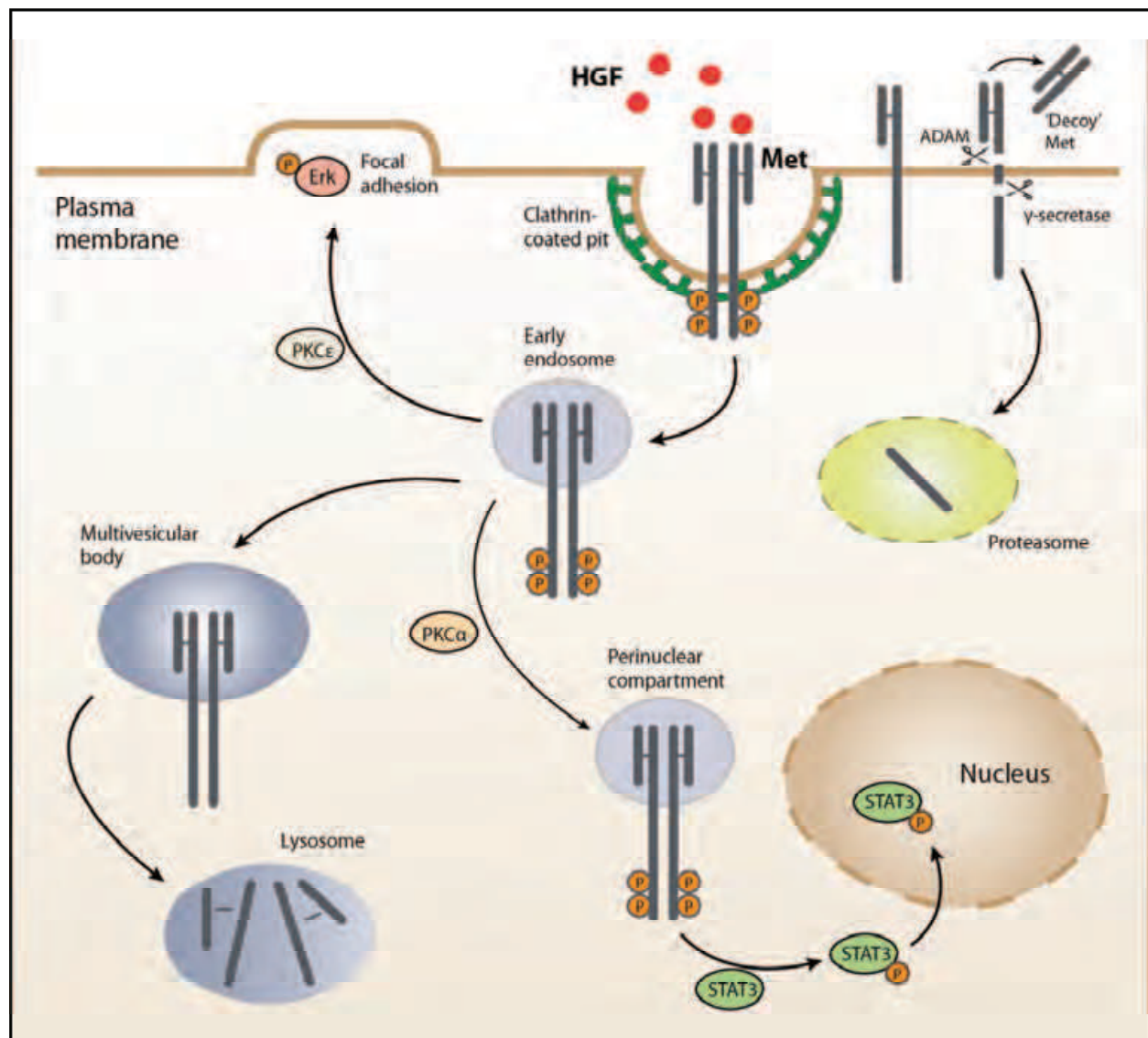


Fig. 3. Mechanisms of Met signaling regulation

There are three biological mechanisms underlying the tumorigenicity of Met: a) the establishment of HGF/c-Met autocrine loops; b) the overexpression of HGF or Met; and c) the presence of activating mutations in the Met receptor (Benvenuti & Comoglio, 2007).

An autocrine mechanism of Met activation is found in some human tumors. For example, osteosarcomas and rhabdomyosarcomas are derived from mesenchymal cells which physiologically produce HGF. Glioblastomas and breast carcinomas are derived from ectodermal tissues that normally express Met but not HGF. Experimental models of HGF/c-Met autocrine loops were also able to generate invasive tumors *in vitro* and in transgenic mice (Boccaccio & Comoglio, 2006).

The most frequent mechanism of Met dysregulation found in human tumors is the overexpression of the receptor or its ligand. A large number of studies showed that HGF and Met are expressed in a wide variety of human tumors and in their metastasis. These include carcinomas of the breast, colon, lung, ovary, liver, kidney, upper gastrointestinal tract, pancreas and prostate but also sarcomas, haematopoietic malignancies, melanomas and glioblastomas (Birchmeier et al., 2003).

It has also been shown that high expression levels of Met and its ligand correlate with increased aggressiveness of tumors and patients poor prognosis (Birchmeier et al., 2003). For example, in colorectal cancer patients Met is a powerful prognostic factor for early stage invasion and metastasis (Kammula et al., 2007). Moreover, in a study including 74 clinical samples of low-grade and high-grade gliomas the authors described a correlation of HGF and Met expression levels with tumor grade (Abounader & Laterra, 2005).

The compelling evidence that links Met with human cancer lies in the *MET*-activating mutations found in hereditary renal papillary carcinoma. These mutations were also found in sporadic tumors such as renal carcinoma, gastric cancer, childhood hepatocellular carcinoma and in head and neck squamous cell carcinomas (Boccaccio & Comoglio, 2006; Lai et al., 2009).

The association between cancer and blood coagulation disorders has been known for many years. In fact, approximately 50% of all patients with malignant tumors and up to 90% of those with metastasis have coagulopathies (Wojtukiewicz et al., 2001). Interestingly, Boccaccio *et al.* showed in a mouse model that activation of the oncogene *Met* induced cancer and a thrombohemorrhagic syndrome through transcriptional upregulation of the procoagulation factors plasminogen activator inhibitor type 1 (PAI-1) and cyclooxygenase-2 (COX-2). Upon a first phase characterized by a hypercoagulation state due to Met signaling activation, the mice developed a hemorrhagic diathesis due to exhaustion of the hyperactivated hemostatic system (Boccaccio et al., 2005). At the early step of this process, hypoxia induces transcription of *Met* that, subsequently, activates the transcription of genes involved in hemostasis, such as *PAI-1* and *COX-2*. The activation of the coagulation cascade will lead to fibrin deposition around cells forming an extracellular matrix that will promote angiogenesis and cell migration (Boccaccio & Comoglio, 2005).

HGF/c-Met signaling also has a role in angiogenesis either by direct influence of c-Met activation in vascular endothelial cells, or by regulation of the expression levels of other angiogenic factors in tumor cells. It was previously shown that the HGF/c-Met interaction stimulates proliferation and migration of endothelial cells *in vitro* and induces blood vessel formation *in vivo* (Bussolino et al., 1992). Zhang *et al.* described the "angiogenic switch" in tumor cells upon HGF stimulation by simultaneous upregulation of the proangiogenic vascular endothelial growth factor (VEGF) and downregulation of thrombospondin 1 (TSP-1), an angiogenesis inhibitor (Y. W. Zhang et al., 2003). This process has distinct mediators: while VEGF is modulated by MAPK, PI3K and STAT3, TSP-1 is targeted only by MAPK. An interesting example of this regulation was found in human glioma cells where stimulation with HGF increased the expression levels of VEGF and tumor-associated angiogenesis. The use of HGF and Met inhibitors in experimental tumor models significantly reduced tumor growth and tumor vessel formation (Abounader & Laterra, 2005).

Recently, a new key player of the HGF/c-Met pathway was described. *Metastasis-associated in colon cancer-1* (*MACC1*) was identified by genome-wide expression analysis in primary and metastatic colon carcinomas. Its expression in human tumor samples was found to be an independent prognostic factor for metastasis formation and metastasis-free survival. The experimental studies showed that *MACC1* promotes proliferation, invasion and HGF-induced scattering *in vitro* and tumor growth and metastasis in xenograft models (Stein et al., 2009). The authors proposed a positive feedback mechanism where *MACC1* acts as a transcriptional regulator of the *Met* gene. The stimulation of the Met receptor with HGF causes the translocation of *MACC1* from the cytoplasm into the nucleus. There, *MACC1* activates the transcription of the *Met* gene by binding to its promoter (Arlt & Stein, 2009).

The increased amounts of Met receptor will be able to bind more HGF molecules thereby enhancing the pathway signaling and promoting cell proliferation, migration and metastasis.

4. HGF/c-Met signaling in medulloblastoma

4.1 Medulloblastoma overview

Medulloblastoma is the most common malignant childhood brain tumor, comprising 20% of all primary brain tumors in the pediatric population (Crawford et al., 2007). It is an embryonal tumor that arises in the cerebellum from primitive pluripotent precursor cells of the ventricular zone and the external granular layer (Hatten & Roussel, 2011).

The 2007 World Health Organization (WHO) classified medulloblastoma in five variants: classic, desmoplastic, anaplastic, large cell and medulloblastoma with extensive nodularity. Clinical data suggests a favorable prognosis for desmoplastic medulloblastoma and a significant worst outcome for the anaplastic subtype (Gilbertson & Ellison, 2008).

Medulloblastoma formation is strongly associated with dysregulation of the pathways involved in the normal development of the cerebellum. The best characterized pathways in medulloblastoma tumorigenesis are the Sonic hedgehog (Shh), Wingless (Wnt) and Notch pathways (Hatten & Roussel, 2011).

Traditionally, patients are stratified into standard risk and high-risk groups according to age, residual tumor and metastatic disease at diagnosis. High-risk patients include those younger than 3 years of age or having a residual tumor or disseminated disease at diagnosis (Packer et al., 2003). In fact, one third of the patients will have metastasis at the time of diagnosis and two thirds will have leptomeningeal spread by the time of relapse (MacDonald, 2008). Moreover, dissemination is the leading cause of treatment failure and the most powerful factor associated with poor survival (Zeltzer et al., 1999).

Recently, Northcott and co-workers described four molecular subtypes of medulloblastoma using gene expression profiling and some genomic features (Northcott et al., 2010). These medulloblastoma subtypes are distinct with respect to the underlying signaling pathway that is dysregulated and the clinical outcome. The Wnt subgroup includes classic medulloblastomas and has a better prognosis. Most tumors in the Shh subgroup are desmoplastic medulloblastomas and also have good prognosis. The other two subgroups, group C and D, are non-Shh/Wnt, and demonstrate *Myc* overexpression as the main feature of group C, and isochromosome 17q as the main feature of group D. Interestingly, group C patients showed a significantly reduced survival, regardless of their metastatic status.

The treatment for standard risk patients includes surgery, craniospinal irradiation and chemotherapy with reported 5-year overall survival of 80%. For patients with metastatic disease the intensified treatment regimens, including high-dose chemotherapy with autologous stem-cell transplantation and non-conventional radiotherapy, have improved prognosis, with 5-year overall survival rates between 50 and 70% (Gajjar et al., 2006; Sanders et al., 2008). Among survivors, a major concern is the long-term sequelae induced by treatments which include endocrinological, neurocognitive, behavioral, motor and sensitive deficits (Armstrong et al., 2009). Therefore, there is a critical need to identify new molecular targets that improve tumor growth suppression while minimizing the side effects of therapy.

4.2 HGF/c-Met pathway in cerebellar development

During embryonic development, the progenitor cells localized in the ventricular zone of the cerebellum (also called primary germinal zone), along the IVth ventricle, migrate radially to give rise to Purkinje cells, neurons of the cerebellar nuclei and different types of cerebellar interneurons. Simultaneously, the progenitor cells in the rhombic lip migrate dorsally to originate the external granule layer (EGL or secondary germinal zone). The peak of proliferation of these cells occurs between postnatal day (P) P5 and P8 in the mouse. Through a tightly regulated mechanism, the progenitor cells in the EGL become postmitotic, differentiate and migrate inwards to give origin to the internal granule layer (IGL), a process that is complete by P20 in the mouse (Marino, 2005).

During the early postnatal period, multiple mitogenic pathways, such as Shh, Wnt and Notch, promote the rapid expansion of progenitor cells in the EGL. It is believed that this vast population of cells includes subgroups of progenitors with distinct genetic properties, that give origin to the different medulloblastoma subtypes (Hatten & Roussel, 2011).

The HGF/c-Met pathway also plays a critical role in cerebellar development. The knockout mice for HGF, Met and SPINT2 are all embryonic lethal (Bladt et al., 1995; Mitchell et al., 2001; Uehara et al., 1995). Comparing the regional expression of HGF and Met in both developing and adult rat brains, Achim and co-workers found expression of HGF in the parietal cortex, striatum and cerebellar deep gray matter in developing but not in adult brain. Abundant expression of Met was also detected in the newborn cortex, thalamus and brainstem (Achim et al., 1997). The analysis of HGF and Met expression in the central nervous system of different mammalian species showed that their neuronal expression is highly conserved during evolution, a sign that they mediate important functions (Jung et al., 1994).

Leraci *et al.* described the expression of Met in the proliferating cells of the external granule layer of the cerebellum and increased proliferation after stimulation of primary cultures of granule cells with HGF. In addition, transgenic mice with partial loss of Met function had a smaller cerebellum with abnormal foliation and balance impairment (Leraci et al., 2002).

HGF has also been proposed to mediate neurotrophic functions during neurogenesis both in the central and peripheral nervous systems. In fact, it was shown that HGF is a chemoattractant and promotes survival of motor neurons in the embryo. Furthermore, stimulation of sensory and sympathetic neurons with HGF enhances survival, differentiation and axonal growth (Maina & Klein, 1999). Exploring the neuroprotective role of HGF, different groups showed that HGF treatment of primary cerebellar granule neurons prevents apoptotic cell death through activation of the PI3K/AKT pathway signaling (Honda et al., 1995; Hossain et al., 2002; L. Zhang et al., 2000).

To further investigate the influence of aberrant HGF/c-Met pathway signaling on cerebellar development and medulloblastoma initiation and progression, our group genetically engineered a transgenic mouse that expresses a constitutively active mutant of human Met, specifically within the cerebellum. We are in the process of characterizing the cerebellar development in the transgenic line as compared to the wild type, and determine the effects of constitutive Met activation in medulloblastoma pathogenesis.

4.3 HGF/c-Met pathway in medulloblastoma formation

HGF/c-Met signaling has an important role in tumorigenesis and metastatic behavior in several human malignancies but its role in medulloblastoma pathogenesis was only recently described.

Studying a series of 14 human medulloblastoma samples by comparative genomic hybridization Tong *et al.* found amplification of the Met oncogene on chromosome 7q in 38.5% of cases (Tong *et al.*, 2004). A separate group showed a correlation between the expression of HGF and Met in human medulloblastoma samples and patient clinical outcome (Li *et al.*, 2005). When they stimulated medulloblastoma cells with HGF there was an activation of downstream effectors, evidenced by Met, MAPK and AKT phosphorylation. Up-regulation of the pathway was also able to induce cell proliferation, cell cycle progression, anchorage-independent growth and resistance to chemotherapy-induced apoptosis in medulloblastoma cell lines. *In vivo* models overexpressing HGF also had increased tumor growth and invasion (Li *et al.*, 2005). More recently, the same group identified an association between HGF/c-Met signaling and c-Myc in medulloblastoma. They found that HGF induced c-Myc expression both at transcriptional and post-transcriptional levels, leading to cell cycle progression, cell proliferation and increased apoptosis (Li *et al.*, 2008b).

Although the anti-apoptotic functions of HGF/c-Met pathway seem to be predominant, Li *et al.* described enhanced cell death in Daoy cell lines after Met activation. Apoptotic cell death can be induced by two different pathways: the intrinsic mitochondrial pathway and the extrinsic death receptor pathway. In malignant tissues, the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has the potential to activate the death receptor pathway upon binding of death receptors DR4 and DR5, which leads to downstream caspase activation and apoptosis (Suliman *et al.*, 2001). Li and co-workers found that increased apoptosis of medulloblastoma cell lines after stimulation with HGF was induced by TRAIL and mediated by DR5 overexpression (Li *et al.*, 2008a). Moreover, the treatment of those cells with a specific c-Met inhibitor (PHA665752) reduced apoptosis indicating that it requires activation of the canonical receptor tyrosine kinase (Li *et al.*, 2008a).

Using an epigenome-wide screening our group identified an inhibitor of HGF/c-Met signaling. SPINT2, a tumor suppressor gene, was downregulated in 73.2% of primary medulloblastoma samples while *Met* was upregulated in 45% of cases. SPINT2 was silenced by promoter hypermethylation in 34.4% of primary tumor samples (Kongkham *et al.*, 2008). A single nucleotide polymorphism (SNP) array analysis identified hemizygous deletions in the SPINT2 locus on chromosome 19q13.2 and gains in the HGF and MET loci on chromosome 7q. The experimental studies using medulloblastoma cells transfected with SPINT2 showed decreased proliferation, migration and anchorage-independent growth *in vitro* and increased survival times in mouse xenografts (Kongkham *et al.*, 2008). Although SPINT2 downregulation has already been implicated in other human cancers (Dong *et al.*, 2010; Morris *et al.*, 2005; Parr *et al.*, 2004) this was the first report to establish its role in medulloblastoma pathogenesis.

Binning *et al.* showed that HGF and Shh cooperate to transform cerebellar neural progenitors in transgenic mice, leading to medulloblastoma initiation and growth (Binning *et al.*, 2008). Furthermore, the treatment of mice bearing Shh+HGF induced tumors with a monoclonal antibody against HGF (L2G7) prolonged survival by increasing apoptosis (Binning *et al.*, 2008). Previous studies had already shown that systemic administration of L2G7 to mouse xenografts of human HGF+/c-Met+ glioblastomas improved survival and reduced tumor growth (Kim *et al.*, 2006).

Knowing that a procoagulant state is often the first manifestation of a malignancy and that it is due to the expression of specific proteins such as tissue factor (TF), Provencal and colleagues analyzed the expression of this protein in human medulloblastoma samples and observed a strong correlation between Met and TF expression levels. Furthermore, the

stimulation of Daoy cells with HGF increased the expression of TF and the treatment of those cells with physiological amounts of TF activator (factor VIIa) increased their migratory potential (Provencal et al., 2009). It was hypothesized that the acquisition of a procoagulant phenotype by medulloblastoma favors its dissemination because the enrichment of the tumor environment with fibrin protects the cancer cells from the immune system and forms a matrix for cell migration (Provencal et al., 2009). The same group found that upregulation of TF upon Met pathway activation was associated with increased resistance to the chemotherapeutic drug etoposide (Provencal et al., 2010). This observation suggested that the combination of anticoagulant drugs and chemotherapy could improve the efficacy of chemotherapeutic agents. In fact, this regimen was already tested in metastatic breast cancer with encouraging results (Falanga et al., 1998). These findings show the importance of the HGF/c-Met pathway signaling in medulloblastoma malignancy. Furthermore, they also provide validation of this pathway as a target for new and promising therapies using small molecular inhibitors and antibodies, some of them already in clinical trials for other cancers.

5. Inhibitors of HGF/c-Met pathway in cancer therapy

The evidence that the HGF/c-Met pathway is involved in the progression and dissemination of several malignancies has generated considerable interest in HGF and Met as major targets in cancer therapy and drug development. Different strategies are being explored and some of them are already being tested in clinical trials. We can consider three main groups of drugs: a) HGF and Met antagonists or competitors; b) Monoclonal antibodies directed against HGF and Met; and c) Small molecule tyrosine kinase inhibitors.

The use of molecular targeted therapies against HGF and Met in medulloblastoma was only recently reported. Our group demonstrated the efficacy of a highly specific small molecular inhibitor (PHA665752) in the treatment of medulloblastoma cell lines by reducing cell proliferation, migration and anchorage-independent growth (Kongkham et al. 2010). Another group used an orally available small molecule inhibitor of Met (SGX523) in medulloblastoma cells and human glioblastoma xenografts. They reported decreased cell proliferation, migration and invasion in the *in vitro* studies and significant reduction of *in vivo* tumor growth (Guessous et al., 2010). The HGF-neutralizing monoclonal antibody, L2G7, was also tested in monotherapy and in combination therapy in genetically engineered mice with medulloblastomas induced by Shh and HGF. The authors reported tumor growth inhibition and increased survival with L2G7 monotherapy (Coon et al., 2010).

Strategies using combined regimens targeting multiple receptor tyrosine kinases are currently under study. This can be achieved in two different ways either by a combination of highly selective agents or by using a single agent that targets multiple specific members of the Met pathway. The use of broad-spectrum agents may have the advantage of reducing drug interactions, but it may also affect other unintended kinases. Stommel *et al.*, studying glioma cell lines, xenografts and human primary glioblastomas, showed simultaneous activation of multiple receptor tyrosine kinases and better responses to combined treatment when compared to monotherapy (Stommel et al., 2007).

We provide a brief summary of the latest advances in HGF/c-Met targeted therapy (Table 1).

5.1 HGF and Met antagonists

HGF and Met antagonists or decoys are molecules that bind to the receptor with high affinity without activation of downstream signaling. The activation of Met by HGF involves

Compound	Mechanism of action	Stage of development	References
Biological antagonists			
NK2	Inhibits HGF activity	Preclinical	Montesano et al. 1998; Otsuka et al. 2000
NK4	Inhibits HGF binding to Met	Preclinical	Kuba et al. 2000; Matsumoto et al. 2008; Matsumoto and Nakamura 2008
Uncleaved HGF	Inhibits proteolytic HGF activation	Preclinical	Mazzone et al. 2004
Decoy Met	Inhibits HGF binding and Met dimerization	Preclinical	Michieli et al. 2004
Antibodies			
AMG102 (Amgen)	Anti-HGF (IgG2)	Phase II trial	Burgess et al. 2006; Gordon et al. 2010; Jun et al. 2007
L2G7 (Galaxy Biotech)	Anti-HGF (IgG1)	Preclinical	Coon et al. 2010; Kim et al. 2006; Li et al. 2009
MetMab (Genentech)	Anti-Met	Phase II trial	Martens et al. 2006
Small molecule inhibitors			
PHA665752 (Pfizer)	Selective inhibitor (Met)	Preclinical	Kongkham et al. 2010; Li et al. 2008a
PF2341066 (Pfizer)	Selective inhibitor (Met and ALK)	Phase II/III	Christensen et al. 2007; Zillhardt et al. 2010; Zou et al. 2007
ARQ197 (ArQule)	Selective inhibitor (Met)	Phase II	Bagai et al. 2010; Munshi et al. 2010
SGX523 (SGX Pharmaceuticals)	Selective inhibitor (Met)	Phase I (discontinued)	Guessous et al. 2010; Y. W. Zhang et al. 2010
XL184 (Exelixis)	Multikinase inhibitor (Met, VEGFR, Ret, Kit, Flt-3, Tie-2)	Phase II/III	http://clinicaltrials.gov
XL880 (Exelixis)	Multikinase inhibitor (Met, VEGFR, PDGFR, Ron, Kit, Flt-3, Tie-2)	Phase II	Qian et al. 2009; http://clinicaltrials.gov
MP470 (Supergen)	Multikinase inhibitor (Met, PDGFR, Ret, Kit, Flt-3)	Phase I	Mahadevan et al. 2007; Qi et al. 2009; Welsh et al. 2009

(VEGFR, vascular endothelial growth factor receptor; Ret, rearranged during transfection; Kit, stem cell factor receptor; Flt-3, FMS-like tyrosine kinase 3; Tie-2, angiopoietin receptor 2; PDGFR, platelet-derived growth factor receptor; Ron, recepteur d'origine nantais)

Table 1. Summary of HGF/c-Met inhibitors.

the dimerization of the receptor upon binding of the two chains of the ligand. HGF has a high affinity site located in the α -chain and a low affinity site in the β -chain, which only becomes accessible after pro-HGF activation (Comoglio et al., 2008). This means that the inactive form of HGF or HGF fragments can interact with Met by binding to the high affinity site but they cannot induce Met signaling because they are unable to promote receptor dimerization.

Examples of HGF competitors are NK2, NK4 and uncleavable HGF. NK2 is a naturally occurring HGF fragment and NK4 is a synthetic truncated form of HGF that contains only the α -chain. This is by far the best studied HGF antagonist and it was shown that it inhibits cell invasion and angiogenesis *in vitro* and in xenografts (Kuba et al., 2000). Uncleavable pro-HGF is an unprocessable form of HGF that competes with active HGF for Met binding and with pro-HGF proteases for HGF proteolytic activation.

Decoy Met is an enzymatically inactive molecule that corresponds to the extracellular domain of the receptor. It interacts with HGF and full-length Met, sequestering the ligand and interfering with the receptor dimerization.

5.2 Monoclonal antibodies directed against HGF and Met

The use of monoclonal antibodies has the following advantages: Specificity against HGF and Met; a relatively longer half-life when compared to other inhibitors; and the potential to induce a host immune response against the tumor cells (Eder et al., 2009).

AMG102 is a fully human IgG2 antibody against HGF that was found to enhance the effects of temozolomide and docetaxel *in vitro* and in xenograft models of gliomas (Jun et al., 2007). A Phase I study used a combination of AMG102 and the antiangiogenic drugs bevacizumab and motesanib in the treatment of patients with advanced solid tumors, showing a stable disease in most patients (Rosen et al., 2008). This molecule has also been tested in Phase II clinical trials for advanced glioblastomas and renal cell carcinomas and a preliminary analysis in glioma patients suggested that AMG102 has limited efficacy as monotherapy (Reardon et al., 2008). Therefore, the most recent clinical trials will use AMG102 in combination therapy (<http://clinicaltrials.gov>). L2G7 is another anti-HGF antibody that proved to be effective reducing subcutaneous and intracranial glioma xenografts and to increase survival (Kim et al., 2006).

The initial efforts to develop antibodies against Met were unsuccessful because they tended to behave as agonists rather than antagonists, due to its bivalent structure that acts as a natural dimerizing agent. To circumvent this problem a 'one-armed' antibody (OA-5D5; MetMAb), consisting of a monovalent Fab fragment, was developed. It binds to Met with high affinity preventing HGF interaction and subsequent downstream signaling. Martens *et al.* infused MetMAb intratumorally, reporting almost complete inhibition of tumor growth in a glioblastoma mouse model (Martens et al., 2006). Phase II clinical trials using MetMAb in combination with bevacizumab and paclitaxel for metastatic breast cancer and with erlotinib for advanced non-small cell lung cancer have been initiated (<http://clinicaltrials.gov>).

5.3 Small molecule tyrosine kinase inhibitors

Small molecule inhibitors target the ATP-binding site of the Met receptor, blocking its transphosphorylation. These molecules can also be classified according to their specificity for Met. Highly selective drugs may not be desirable as inhibition of multiple kinases may

be more efficient and reduce the development of resistance. On the other hand, off-target inhibition of essential kinases may also be deleterious. With the recent advances in research and the ongoing clinical trials the small molecule inhibitors have emerged as promising drugs (Naran et al., 2009).

PHA665752 is a Met selective inhibitor that was found to be effective in tumor cell lines and xenografts, particularly in a subset of cancers with amplification of the Met gene (Kongkham et al., 2010; Smolen et al., 2006). Due to its low oral bioavailability another drug (PF2341066) with identical structure but more favorable pharmacokinetic properties was designed. PF2341066 selectively targets Met and anaplastic lymphoma kinase (ALK) and was shown to have antitumor cytoreductive activity and antiangiogenic activity in several cancer models (Christensen et al., 2007; Zillhardt et al., 2010; Zou et al., 2007). A Phase II study in non-small-cell lung cancer reported encouraging results with a disease control rate of 87% (Mayor, 2011). The drug is now in Phase III trials. Interestingly, PF2341066 is also being tested in Phase I/II studies in children with recurrent solid tumors, primary central nervous system tumors and anaplastic large cell lymphoma (<http://clinicaltrials.gov>).

ARQ197 is a highly selective, non-ATP competitive drug with reported clinical activity in several types of solid tumors. A Phase II trial in patients with non-small-cell lung cancer reported improved survival in patients treated with ARQ197 and erlotinib when compared to erlotinib monotherapy (Mayor, 2011).

SGX523 is an orally available ATP-competitive molecule with high selectivity for Met. Although the initial results with *in vitro* and *in vivo* models of medulloblastomas and gliomas looked promising because of its efficacy in reducing tumor growth, the drug was discontinued from a Phase I trial due to renal toxicity (Diamond et al., 2010).

XL184 and XL880 are orally available, non-selective inhibitors, with high binding affinity to both Met and VEGFR and to a lesser extent to other receptor tyrosine kinases such as PDGFR, Ret, Kit, Flt-3 and Tie-2 (Liu et al., 2010). XL184 is being evaluated in a Phase III study in patients with advanced medullary thyroid cancer and in Phase II studies in patients with glioblastoma multiforme and non-small-cell lung cancer that has progressed after previous benefit with erlotinib. XL880 has been tested in Phase II clinical trials in metastatic gastric cancer, papillary renal cell carcinoma and head and neck squamous cell cancer (<http://clinicaltrials.gov>).

MP470 is a multi-kinase inhibitor, orally available, that was reported to radiosensitize glioblastoma cell lines, through the suppression of RAD51, a DNA repair related protein (Welsh et al., 2009). Additional Phase I clinical studies, currently underway, use MP470 in monotherapy or in combination with standard chemotherapies in patients with metastatic solid tumors and lymphoma (<http://clinicaltrials.gov>).

6. Conclusion and future directions

The HGF/c-Met signaling pathway plays a significant role in cancer and has emerged recently as a promising target in the treatment of several malignancies. It was shown that HGF and Met are key players in cerebellum development and that their dysregulation is involved in medulloblastoma formation and progression.

Advances in understanding the molecular mechanisms and genetic profiles underlying the different subtypes of medulloblastoma created an urgent need for new and less toxic targeted therapies. HGF/c-Met inhibitors used in the treatment of gliomas *in vitro* and *in*

in vivo showed efficient reduction in tumor growth and are, therefore, being evaluated in clinical trials. Our preliminary data using a Met selective inhibitor in medulloblastoma cell lines showed that the HGF/c-Met pathway is a novel and promising therapeutic target in this disease.

In the future we will test a panel of available HGF and Met inhibitors using orthotopic xenograft models and our transgenic medulloblastoma mouse model. We hope that the results of our pre-clinical studies will provide the basis for future clinical trials where the HGF and Met inhibitors could synergize with current therapies to increase survival and improve the quality of life of children with brain tumors.

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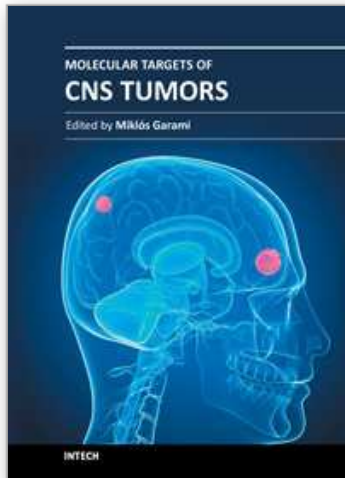
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