

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

**4,800**

Open access books available

**122,000**

International authors and editors

**135M**

Downloads

Our authors are among the

**154**

Countries delivered to

**TOP 1%**

most cited scientists

**12.2%**

Contributors from top 500 universities



**WEB OF SCIENCE™**

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.

For more information visit [www.intechopen.com](http://www.intechopen.com)



# Midkine Signaling in Glioblastoma: A Novel Developmental Drug Target?

Ayhan Bilir<sup>1</sup> and Mine Erguven<sup>2</sup>

<sup>1</sup>*Istanbul University, Istanbul Faculty of Medicine, Department of Histology and Embryology,*

<sup>2</sup>*Yeni Yüzyıl University, Faculty of Medicine, Department of Clinical Biochemistry, Turkey*

## 1. Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults and is a complicated disease to treat. The current standard therapy includes surgical resection, followed by a combination of radiation and chemotherapy with several drugs. However, resistance and recurrence are quite common, so we continue to investigate more effective treatments both for initial therapy and recurrence by searching novel neglected molecular targets as midkine. This article will review the significance of midkine in therapy for newly-diagnosed and recurrent glioblastomas.

## 2. Glioblastoma

In adults, GBMs are the most lethal and most frequent malignant brain tumors. Approximately, half of all primary brain tumors are gliomas. Gliomas arise from glial cells, the building-block cells of the connective and supportive, tissues in the central nervous system. The common gliomas are diffuse gliomas which infiltrate throughout the brain parenchyma. These are classified histologically and/or ultrastructurally as astrocytomas, oligodendrogliomas, and oligoastrocytomas. They are graded on a World Health Organization (WHO) classification system scale of I to IV according to their degree of malignancy based on different histological features and genetic alterations. Grade I tumors are benign and can be cured if they can be surgically resected; grade II tumors are incurable with surgery because of their early diffuse infiltration of the surrounding brain, and long treatment regimens are needed to treat this disease completely; grade III tumors have increased anaplasia and proliferate over grade IV tumors and are more rapidly fatal; grade IV tumors possess advanced features of malignancy, and are resistant to radio/chemotherapy. Hence, they are characterized with poor prognosis resulting in the death within ~9-12 months. Grade I, II, III, and IV designation are pilocytic astrocytoma, low grade astrocytoma (LGA), anaplastic astrocytoma, and GBM, respectively. The most frequent subtypes are glioblastoma (47%) and grade II-III astrocytoma (23%), followed by oligodendroglioma and mixed glioma (Furnari et al., 2007; Krakstad and Chekenya, 2010).

Patients suffered from GBM generally have a dismal prognosis, with an average survival time of only 9-12 months from their diagnosis, and thus GBMs can be named as “terminator”. GBM accounts for ~ 50% of adult gliomas; and up to 10% of pediatric gliomas are either anaplastic astrocytomas or GBMs. Cases of GBMs are distributed over a broad range of ages, with an average age of 53 years at diagnosis. Prognostic factors include age and post-operative physical performance status. The tumors of older patients are more aggressive and more resistant to treatment. The patients who are alive just 3 to 5 years following diagnosis are defined as “long-term survivors” and they are rare. Younger age than the average of 53 years is usually the only common feature of long-term survivors (Furnari et al., 2007; Krakstad and Chekenya, 2010; Ouant and Wen, 2010).

Important characteristics of GBMs are aberrant cellular proliferation, diffuse infiltration, propensity for necrosis, robust angiogenesis, high resistance to apoptosis, and genomic instability. The intratumoral heterogeneity combined with a putative cancer stem cell (CSC) subpopulation and incomplete atlas of epigenetic lesions are the reasons of poor prognosis/high tumoral resistance against chemotherapeutics and recurrence. GBMs have been subdivided into the primary (*de novo*) and secondary (progressive) GBMs according to their clinical evaluation. Primary GBMs are commonly detected as subtypes, and tend to occur in older patients above the age of 45 years. Primary GBMs presents in an acute *de novo* manner without any evidence of prior clinical disease. In contrast, secondary GBMs are quite rare and commonly detected in younger patients below the age of 45 years. In addition, the latter initially present with lower grade astrocytomas and latterly ~70% of grade II gliomas transform into GBMs within 5-10 years of the initial diagnosis, regardless of prior therapy. Primary and secondary GBMs show differences in their clinical characteristics and genetic profiles [different transcriptional patterns and frequency of specific mutations as the mutations of tumour suppressor genes retinoblastoma (Rb) and p53 result in DNA copy number aberrations]. However, they also have similarities, which are morphologically indistinguishable and show poor prognosis (Furnari et al., 2007; Cheng et al., 2010; Ouant and Wen, 2010).

Glioblastomas circumvent the blockage of tumour suppressor genes [p53, phosphatase and tensin homolog deleted on chromosome 10 (PTEN), and Rb] on positive regulators of cell division, survival and motility. These positive regulators are receptor tyrosine kinases [RTKs, i.e. Platelet derived growth factor receptor (PDGFR), Epidermal growth factor receptor (EGFR), Vascular endothelial growth factor receptor (VEGFR)], growth factors [i.e. platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF)], cell adhesion molecules (i.e. integrins) and their two major downstream signaling pathways [i.e. mitogen activated protein kinase (MAPK), phosphoinositide-3 kinases (PI3Ks)]. Molecular pathogenesis of primary GBMs present (1) mutations of INK4aARF, PTEN, EGFR, loss of heterozygosity (LOH) of chromosome 10p and 10q, (2) amplifications of EGFR, Cyclin D1/3, murine double minute 2 and 4 (MDM2 and MDM4), and (3) overexpressions of Bcl2-like-12 (Bcl2L 12) (~95 %), cyclin D 1/3. In contrast, molecular pathogenesis of secondary GBMs present (1) mutations of tumor suppressors p53, Rb, PTEN (~10 %), loss of chromosomes 10q, 11p, 19q, (2) amplifications of cyclin dependent kinases 4/6 (CDK4/6), and (3) overexpressions of PDGFR, PDGF, CDK4/6 (Furnari et al., 2007; Krakstad and Chekenya, 2010).

Glioblastomas, the most highly vascular of all solid tumors and microvascular hyperplasia, define both the histological phenotype of primary and secondary GBM. Although primary and secondary GBMs possess different genomic profiles, they form a final common angiogenesis pathway involving hypoxia inducible factor (HIF) and non-HIF-dependent downstream effectors such as VEGF, PDGF, stromal cell-derived factor-1 (SDF-1), endostatin, and thrombospondin 1 and 2 (TSP-1 and TSP-2). Because of their significant roles in GBMs' molecular pathogenesis, these molecules/pathways are accepted as "major targets" for the treatment of GBMs (Furnari et al., 2007; Krakstad and Chekenya, 2010). The poor prognosis despite aggressive treatment indicates the need to establish novel targets for molecular intervention.

### 3. Midkine

Midkine also known as MDK, FLJ27379, and NEGF2 is a heparin-binding cytokine or a growth factor or an angiogenic factor with a molecular weight of 13 kDa. Midkine binds to oversulfated structures in heparan sulfate and chondroitin sulfate. MDK is the founding member of a family, which is composed of only two members in humans. The other member is pleiotrophin (PTN), also called HB-GAM (Deuel et al., 2002; Rauvala and Peng, 1997). MDK is 50% homologous to PTN at the amino acid level and shares with PTN the genomic organization (Rauvala and Peng, 1997; Muramatsu et al., 1993; Owada et al. 1999) and predicted protein structure (Maeda et al., 1999; Sato et al., 2001).

The structure of MDK is mainly composed of two domains linked by disulfide bonds (Fabri et al., 1993). The C-domain possess basic heparin-binding activity which is responsible for the mechanism of action (Muramatsu et al., 1994). Each domain of MDK has also homology to the thrombospondin Type I repeat (Kilpelainen et al., 2000). Two domains are composed of three anti-parallel  $\beta$ -sheets (Iwasaki et al., 1997). The C-domain has two clusters of basic amino acids named as Cluster-1 and -2. These clusters are required for heparin-binding activity (Asai et al., 1997; Iwasaki et al., 1997; Akhter et al., 1998). MDK forms dimers via spontaneous association and transglutaminase stabilize dimers through crosslinking process (35). MDK is seemed to require dimerization for its activity (Kojima et al., 1997). After dimerization, Cluster-2 forms a fused strong binding site (Iwasaki et al., 1997).

Midkine was originally reported to be the product of a retinoic acid-responsive gene during embryogenesis (Takei et al., 2001). The expression of MDK was high during embryogenesis, but interestingly, MDK is not detectable in healthy adults and only re-appears in the body as a part of the pathogenesis of diseases (Muramatsu et al., 2010). MDK promotes proliferation (Muramatsu et al., 2006), migration (Maeda et al., 1999), anti-apoptotic manner (Quin et al., 2011), mitogenesis (Dai 2009), transforming (Nobata et al., 2005), and angiogenesis (Gustavsson et al., 2008) various cells. It has significant roles in reproduction, repair and in epidemiology of many diseases as rheumatoid arthritis (Maruyama et al., 2004), multiple sclerosis (Wang et al., 2008), hypertension and renal disease (Kodamatsu 2010), and cancer (Gustavsson et al., 2008). The most intriguing feature of MDK is its massive expression in advanced tumors with high frequency (Qin Li et al., 2011; Kemik et al., 2010). Previous reports showed that the blood MDK level is frequently elevated with advance of human carcinomas, decreased after surgical removal of the tumors (Kemik et al., 2010; Ota et al., 2008; Lucas et al., 2010).

Glycosaminoglycan-recognizing activity of human MDK through its C-domain as heparan sulfate trisulfated unit and chondroitin sulfate E unit is important in its mechanism of action. Heparin inhibits MDK activity. Proteoglycans like receptor-like protein tyrosine phosphatase-z (PTPz) (Maeda et al. 1999) syndecans (Mitsiadis et al., 1995), glypican-2

(Kurosawa et al., 2001), PG-M/versican (Zou et al., 2000) and neuroglycan C (Ichihara-Tanaka et al., 2006) have strong affinity to MDK. Chondroitin sulfate proteoglycan PTPz is a component of the MDK receptor. Low density lipoprotein receptor-related protein (LRP) (Muramatsu et al., 2000),  $\alpha 4\beta 1$ -integrin and  $\alpha 6\beta 1$ -integrin (Muramatsu et al., 2004) also serve as MDK receptors. These proteins and PTPz form a receptor complex of MDK. After the complex formation with PTPz and integrins, MDK starts downstream signaling systems as Src family kinases and tyrosine phosphorylation, respectively (Muramatsu et al., 2000; Maeda et al. 1999). Increased tyrosine phosphorylation of paxillin leads to migration at osteoblast like cells and followed by suppression of caspases, activation of PI3 kinase and mitogen activated protein (MAP) kinase takes part in survival (Muramatsu et al., 2000; Maeda et al. 1999; Owada et al., 1999; Ohuchida et al., 2004). The previous reports showed that when MDK binds to  $\alpha 6\beta 1$ -integrin and tetraspanin, and induces tyrosine phosphorylation of focal adhesion kinase (FAK) followed by activation of paxillin and signal transducer and activator of transcription alpha (STAT1 $\alpha$ ) pathway, it increases migration and invasion at human head and neck squamous cell carcinoma cells in vitro (Huang et al., 2008). Due to phosphorylation of STAT3 by MDK, the proliferation of postconfluent 3T3-L1 cells are stimulated and this leads to adipogenesis (Cernkovich et al., 2007). Notch2 reserves an another receptor for MDK and acting through the janus kinase 2 (Jak2)/STAT3 signalling pathway, MDK leads to epithelial-mesenchymal transition (EMT) in immortalized keratinocytes. Both MDK and PTN plays important role in EMT and neurogenesis during organogenesis process in embryonal development (Huang et al., 2008) Previous reports proposed that Anaplastic lymphoma kinase (ALK) can be included in the receptor group of MDK (Stoica et al., 2002). Unpublished observations of Muramatsu and coworkers, ALK also involves in the MDK complex with LRP and integrins that it is recruited to the receptor complex and plays roles in MDK signaling (Muramatsu 2010). After activation by MDK, ALK phosphorylates insulin receptor substrate-1, activates MAP kinase and PI3 kinase leading to transcriptional activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) (Stoica et al., 2002).

MDK binds to nucleolin, a nuclear protein which is also located at the cell surface and functions as a shuttle to the nucleus (Take et al, 1994; Dai 2009). A component of the MDK receptor LRP has major function as endocytose and delivering its ligands to lysosomes for degradation or catabolism (Hussain et al., 1999; Krieger et al., 1994). LRP takes part in internalization of MDK (Shibata et al., 2002). MDK is not internalized in LRP-deficient cells, whereas transfection of a LRP expression vector can restore MDK internalization and subsequent nuclear translocation, suggesting that LRP binds to heparin-binding growth factor, MDK, and mediates nuclear targeting by MDK. After this internalization, nucleolin transfer cytoplasmic MDK to the nucleus (Shibata et al., 2002). With respect to nuclear targeting by MDK, laminin-binding protein precursor (LBP) binds to MDK and is cotranslocated with MDK into nuclei (Owada et al., 1999). MDK may use both nucleolin and LBP precursor as shuttle proteins, revealing a novel role of LRP in intracellular signaling by its ligand, and the importance of nucleolin and LBP in the process of nuclear target of MDK. MDK transferred to the nucleolus is involved in the synthesis of ribosomal RNA (Dai et al., 2008). Unpublished observation by Muramatsu, H. and coworkers, translation initiation factor (eIF3) is can be an MDK-binding protein in the embryonic brain (Muramatsu 2010).

#### 4. Midkine and glioblastoma

In the central nervous system, MDK is expressed by astrocytes in the fetal brain (Satoh et al., 1993), and its expression is developmentally regulated, decreasing progressively to an

undetectable level as the fetus matures (Kodamatsu et al., 1990; Mitsiadis, et al., 1995). Previous reports showed that increased levels of MDK expression correlate with the progression of human astrocytomas, MDK mRNA and protein expression levels were higher in high-grade astrocytomas as anaplastic astrocytomas and GBMs than in low-grade astrocytomas (oligodendroglioma, ependioma, schwannoma, meningioma and pituitary adenoma) (Mishima et al., 1997). These reports conclude that MDK correlates with the poor prognosis of GBM. Stoica et al. showed that MDK activates PI3-kinase and MAP kinase signal transduction in U87MG human glioblastoma cells which express ALK protein (Stoica et al., 2002). They showed that MDK is also unable to stimulate Akt phosphorylation upon reduction of ALK. In their report they revealed that in contrast with the diminished PTN and MDK signals after reduction of ALK, Akt phosphorylation in the same cells via a different tyrosine kinase receptor, the platelet-derived growth factor receptor (PDGF-R), was not altered by the reduction of ALK levels (Powers et al., 2002). Interestingly, in the U87MG cells mitogen activated protein kinase (MAPK) is activated constitutively and remains unaffected by the ALK reduction or by MDK addition.

In contrast to Stoica and coworkers, Grzelinski and coworkers determined no mRNA levels of ALK and RPTP  $\beta/\zeta$  levels, but high mRNA levels of MDK and PTN were determined in another human glioblastoma cell lines named T98G (Stoica et al., 2002; Grzelinski et al., 2009). This condition is also same for human glioblastoma cell lines named G55T2. U118 GBM cells possess high mRNA levels of ALK, low mRNA levels of MDK and RPTP  $\beta/\zeta$  but no mRNA levels of PTN are detected. All cell lines derived from human GBMs are different. In the light of report by Grzelinski and coworkers we can conclude that MDK levels at GBM may not only affected by activity of ALK.

GBM has a complex tumor structure consisting of accumulating tumors cells, abnormal vessel and necrotic debris. The increasing tumor mass leads to increased capillary and venous collapse (Merlo, 2003). The new formed vessels are structurally and functionally abnormal, and leaky, leading to edema, and low oxygen tension (Bani-Yaghoub et al., 2006). High  $O_2$  tension degrades hypoxia inducible factor-1 alpha (HIF-1 $\alpha$ ) and consequently promotes differentiation or apoptosis, HIF-1 $\alpha$  maintains at lower  $O_2$  tension this augments signal transduction pathways leading to promote self-renewal (Panchision, 2009). Hypoxia induces MDK expression through the binding of to a hypoxia responsive element in the MDK promoter.

Survivin, an antiapoptotic protein, has been found to be overexpressed in up to 79% of astrocytic tumors (Kajiwara et al., 2003; Yamada et al., 2003; Chakravarti et al., 2002). The expression of this gene correlates with grade and is present in 90% of GBMs. The activity of this promoter is also enhanced by hypoxia, commonly found in rapidly growing tumors like high grade gliomas (Yang et al., 2004). Survivin seems to play an important role in the oncogenesis and progression of these tumors (Kleinschmidt - DeMasters et al., 2003; Das et al., 2002). This is suggested by its expression pattern and by the fact that patients with survivin positive astrocytic tumors have significantly shorter overall survival times compared with patients who have survivin negative tumors. Ulasov and coworkers showed that Survivin, CXCR4 and midkine mRNAs are overexpressed in brain tumors compared to normal tissue (Ulasov et al., 2007). Although hypoxia activation both on survivin and MDK, high survivin expression detected human GBM cell lines (U87MG and U373MG) showed significantly decreased the expression of MDK mRNA in comparison to others (U118). We can conclude that hypoxia induced activation depends on the genetic profile of tumour and this also strengthen the reason of GBM complexity during therapies.

Notch2 has been suggested to drive embryonic brain tumor growth, however Notch3 has been implicated in choroid plexus tumors (Solecki et al., 2001; Dang et al., 2006). The frequency and the intensity of Notch2 expression is higher than that of Notch1 in GBM and in medulloblastoma (Sivasankaran et al., 2009; Fan et al., 2004). As a consequence of local genomic amplifications at the **Notch2** locus in both brain tumor types, this may also be linked to the later persistence of **Notch2** expression in postnatal mouse brain (Tanaka et al., 1999). Previous report showed that Notch1 regulates transcription of the epidermal growth factor receptor gene **EGFR**, known to be overexpressed or amplified in GBM, through TP53 (Purow et al., 2008). Reports showed that there is a direct correlation between p53 and MDK levels. Consistently, transcription of Notch signaling mediator genes are significantly overexpressed in the molecular subset of GBM with **EGFR** amplification (Brennan et al., 2009). Notch signaling activates the major GBM signalling pathway. Subsets of gliomas (even with distinct histologies) with impaired Notch signaling result in slower progression.

The most frequent genetic alteration occurring in GBM is genomic amplification of **EGFR** (Liebermann et al 1985a, 1985b). Consistently, EGF is the major proliferation pathway in GBM, mediated by activation of the RAS-RAF-MEK-ERK and the PI3K-AKT-mTOR cascades (Merlo 2003). Interestingly, mTOR has recently been shown to activate Notch signaling in lung and kidney tumor cells through induction of the Stat3/p63/Jagged signaling cascade (Ma et al., 2010). Lino and coworkers proposed this cross-talk for GBM that this suggests potential creation of a positive feedback loop between Notch and EGF signalling (Lino et al., 2010). The most frequent GBM subset consists of the association of **EGFR** amplification, homozygous deletions at the cyclin dependent kinase 2A (**CDKN2A**) locus, and **TP53** mutations (Ohgaki et al., 2004). Notch activates expression of EGFR via TP53 (Purow et al., 2008), thus Notch is expected to stimulate the main GBM proliferation pathway. In addition, Notch also **transactivates** the gene for the EGFR-related ERBB2 in a DTX1-dependent manner (Patten et al., 2006). Notch-2 serves another receptor for MDK and so cross-talk between MDK and Notch-2 has been also shown to be a mediator of chemotherapy resistance to neighboring cells in GBM (Ikushima et al., 2009).

Tumors resistance to chemotherapy occurred when a subset of cells overexpress drug transport proteins, possess receptor changes for the commitment of drug binding and lack of ability to commit apoptosis. Mirkin and coworkers investigate the cytoprotective relationship between resistant and nonresistant cells in tumors which both accomplish to survive against drug cytotoxicity in human neuroblastoma (SKN-SH) and osteosarcoma (Saos2) (Mirkin et al., 2005). They hypothesized that drug-resistant cells may secrete in their culture medium factors able to protect sensitive cells from cytotoxicity of drug. They showed that expression of MDK was only detected in drug resistant cells and midkine-enriched fractions exert a significant cytoprotective effect against doxorubicin in the wild-type drug-sensitive cells. In addition, they transfected these cells with MDK gene resulting in decreased response to DXR due to activation of AKT pathway and suppression of caspase pathway. They concluded that the existence of intercellular cytoprotective signals such as the one mediated by MDK, originating from cells with acquired drug resistance to protect neighboring drug-sensitive cells and thus contribute to development of resistance to chemotherapy. They didn't mention about the direct effect of MDK on drug efflux transporters.

Hu and coworkers explored the possible effects of MDK gene on the chemotherapeutic drugs efflux and they concluded that there was powerful drug efflux ability in lymphoblastic leukemia cells with high MDK gene expression (Hu et al., 2010). They

proposed that MDK gene expression regulates drug efflux upstream of the p-glycoprotein (P-gp) and the other transporter proteins in this cell line. Previous reports showed that the expression of is higher than expression of p-gp in T98G (Rosenbaum et al., 2005). In our study, we investigated whether the combination of an antineoplastic imatinib mesylate (IM) and an antitussive noscapine (Nos) with new identified chemotherapeutic effects, can be an effective GBM treatment and the possible role of midkine (MDK) in this treatment by using human GBM cells named T98G cells (Unpublished data by Erguven et al.). The lowest MRP-1 levels, but highest MDK levels were detected in the combination group. The lowest MDK levels were detected in IM group especially at the 72<sup>nd</sup> hr ( $p < 0.05$ ), but IM takes second place at MRP-1 inhibition. The highest and the lowest p-170 levels were detected at the IM group ( $p < 0.05$ ) and the Nos group ( $p < 0.05$ ), respectively. Thus, we can conclude that drug efflux ability was not correlated with MDK levels in this experiment.

Yao and coworkers revealed that MDK is expressed in mouse embryonic stem cells (mESCs), human embryonic stem cells (hESCs) and mouse embryonic fibroblasts (MEFs) (Yao et al., 2010). In their study, MDK promotes proliferation and self-renewal of both mESCs and hESCs. Further study by Yao and coworkers showed that the promoted growth of mESCs by MDK is occurred through inhibiting apoptosis while accelerating the progression toward the S phase, and MDK leads to enhancement of mESC self-renewal through PI3K/Akt signaling pathway. They concluded that MDK plays profound roles in ESCs and MDK/PTPzeta signaling pathway is a novel pathway in the signal network maintaining pluripotency of ESCs. Their results extend gives information about the pluripotency control of ESCs and the relationship between ESCs and cancers. Huang and coworkers and the others demonstrated that a highly tumorigenic subpopulation of cancer cells called GBM stem cells (GSCs) promotes therapeutic resistance (Huang et al., 2010). Huang and co-workers showed that GSCs stimulate tumor angiogenesis by expressing elevated levels of VEGF and contribute to tumor growth. In addition, stem cell-like cancer cells (cancer stem cells) have been shown to promote metastasis. MDK was found to be expressed in neural precursor cells, which consist of neural stem cells and the progenitor cells which has been translated into a useful therapeutic strategy in the treatment of recurrent or progressive GBMs (Zhou et al., 2006).

## 5. Midkine inhibitors

After the determination of significant role of MDK in carcinogenesis, the inhibition of MDK through the synthesis or action become a highlighting target for investigators. Previous report by Dai and coworkers showed that MDK inhibitors as antisense oligonucleotides potentiated the cytotoxicity of drugs and decreased their inhibition concentration value 50 ( $IC_{50}$ ) in hepatocellular carcinoma cells and in situ hepatocarcinoma models (Dai 2009). Other reports showed that antisense oligonucleotides to MDK inhibit the growth of mouse colorectal carcinoma cells in vitro and suppress the growth of the tumor in nude mice (Takei et al., 2001). Takei and coworkers showed combinational antitumor effect of siRNA against midkine and paclitaxel on growth of human prostate cancer xenografts (Takei et al., 2006).

Polyclonal anti-MDK antibodies inhibit the growth of tumor cells in vitro, however many monoclonal antibodies to MDK effected weakly due to internalization MDK. Another type of inhibitors tested for MDK inhibition are aptamers and like monoclonal antibodies, they don't inhibit growth of tumor cells efficiently (Wang et al., 2008). A low molecular weight compounds were seemed promising MDK inhibitors. Matsui and coworkers found two



trifluoro compounds: one (PubChem 4603792) is 2-(2,6-dimethylpiperidin-1-yl)-4-thiophen-2-yl-6-(trifluoromethyl)pyrimidine, and the other has a related structure that inhibits MDK effectively without cytotoxic effects at osteoblast-like cells not at cancer cells (Matsui et al., 2010). Last report by Sakamoto and coworkers in 2011 showed that the premature ligand-receptor interaction during biosynthesis limits the production of MDK and its receptor LDL receptor-related protein 1 (LRP1) (Sakamoto et al., 2011). They utilized an endoplasmic reticulum (ER)-retrieval signal and a LRP1 fragment, which strongly bound to midkine and the LRP1-specialized chaperone RAP, to construct an ER-trapper. The ER-trapper efficiently trapped midkine and RAP, and mimicked the premature ligand-receptor interaction (maturation suppression of the ligand and receptor) and also diminished the inhibitory function of LRP1 on cell migration by PDGF in human colorectal carcinomas. Up to date, we have not seen any application of these therapeutic approaches mentioned above for GBM.

In addition to these therapeutic applications, antineoplastic and non-antineoplastic drugs which were used in clinic efficiently for many years, were investigated for their role as MDK inhibitor (Erguven et al., 2011; Bilir et al., 2010). In our another study, we combined a well known microtubule inhibitor drug vinorelbine with antiproliferative drug lithium chloride and antidepressant drug clomipramine for neuroblastoma treatment *in vitro* and showed their novel mechanism of action as MDK inhibitor (Bilir et al., 2010). Rawnaq and coworkers showed that IM, a well known tyrosine kinase inhibitor, decreases MDK levels in the serums of patients with GIST (Rawnaq et al., 2010). In concomitant with these results we showed that IM also decreased MDK levels in human GBM cell lines T98G (Erguven et al., 2011). In addition we also revealed novel mechanism of action of an antitussive drug with new antineoplastic effects as MDK inhibitor and effect of MDK in the antagonism of IM with Nos in T98G cells (Erguven et al., 2011).

## 6. Concluding remarks and discussion

Glioblastoma is the most common and the most aggressive primary brain tumor against conventional therapies, that is, radiotherapy, chemotherapy, surgery and their combinations which have been being resulted in only transient clinical response followed by tumor resistance/recurrence, without any significant improvement of patient survival and life quality. MDK with significant roles at proliferation, survival and resistance, invasion, neovascularization and recurrence holds a promise of being a particularly appropriate target to fight against GBM. Recent studies indicate that cancer stem cells share core signaling pathways with normal somatic or embryonic stem cells, but also display critical distinctions that provide important clues into useful therapeutic targets. High MDK levels also plays critical role in this distinction (Yao et al., 2010). These are very highly infiltrative cancers often invade into normal brain tissues preventing surgical resection, and GSCs are responsible for this aggressive invasive phenotype, so targeting GSCs can effectively reduce tumor resistance and recurrence. All together patient outcome can be improved with the future development of novel therapies interfering with identified MDK signalling pathways. Novel therapies applied with MDK inhibitors can serve more selective and less cytotoxic manner with maximum efficiency and without resistance and/or recurrence as we mentioned above for low molecular weight compounds. All these are needed further investigations. Complexity of GBM can be seen basically in different human GBM cell lines derived from patients belonging to different populations in terms of MDK levels and its receptors. Therefore, individual based therapy should be administered.

## 7. References

- Akhter, S., Ichihara-Tanaka, K., Kojima, S., Muramatsu, H., Inui, T. et al. (1998). Clusters of basic amino acids in midkine: roles in neurite-promoting activity and plasminogen activator enhancing activity. *The Journal of Biochemistry*, Vol. 123, No.6, (June 1998), pp. 1127-1136.
- Erguven, M., Bilir, A., Yazihan, N., Ermis, E., Sabanci, A., Aktas, E., Aras, Y., Alpman, V. (2011) Decreased therapeutic effects of nescapine combined with imatinib mesylate on human glioblastoma in vitro and the effect of midkine. *Cancer Cell International*, Vol.11, No.1, (Jun 2011), pp. 18.
- Asai, T., Watanabe, K., Ichihara-Tanaka, K., Kaneda, N., Kojima, S. et al. (1997) Identification of heparin-binding sites in midkine and their role in neurite-promotion. *Biochemical and Biophysical Research Communications*, Vol. 236, No 1., (July 1997), pp.66-70.
- Bani-Yaghoub, M., Tremblay, R.G., Lei, J.X., Zhang, D., Zurakowski, B., et al. (2006). Role of Sox2 in the development of the mouse neocortex. *Developmental Biology*, Vol. 295, No.1, (July 2006), pp.52-66.
- Bilir, A., Erguven, M., Yazihan, N., Aktas, E., Oktem, G. et al. 2010). Enhancement of vinorelbine-induced cytotoxicity and apoptosis by clomipramine and lithium chloride in human neuroblastoma cancer cell line SH-SY5Y. *Journal of Neurooncology.*, Vol.100, No.3, (December 2010), pp.385-95.
- Brennan, C., Momota, H., Hambardzumyan, D., Ozawa, T., Tandon, A., et al. (2009). Glioblastoma subclasses can be defined by activity among signal transduction pathways and associated genomic alterations. *Public Library of Science* since, Vol. 4, No. 11, (November 2009), pp. e7752.
- Cernkovich, E. R., Deng, J., Hua, K., Harp, J. B. (2007). Midkine is an autocrine activator of signal transducer and activator of transcription 3 in 3T3-L1 cells. *Endocrinology*, Vol.148, No.4, (April 2007), pp.1598-1604.
- Chakravarti, A., Noll, E., Black, P.M., Finkelstein, D.F., Finkelstein, D.M. et al. (2002) Quantitatively determined survivin expression levels are of prognostic value in human gliomas. *Journal of Clinical Oncology*, Vol. 20, No.4 (February 2002), pp.1063-8.
- Cheng, L., Bao, S., Rich, J.N. (2010). Potential therapeutic implications of cancer stem cells in glioblastoma. *Biochemical Pharmacology*, Vol.80, No.5, (September 2010), pp.654-65.
- Dai, L.C. (2009). Midkine translocated to nucleoli and involved in carcinogenesis. *World Journal of Gastroenterology*, Vol.15, No.4, (January 2009), pp.412-6.
- Dai, L.C., Shao, J. Z., Min, L. S., Xiao, Y. T., Xiang, L. X. et al. (2008) Midkine accumulated in nucleolus of HepG2 cells involved in rRNA transcription. *The World Journal of Gastroenterology*, Vol. 14, No. 40, (October 2008), pp.6249-6253.
- Dang, L., Fan, X., Chaudhry, A., Wang, M., Gaiano, N., Eberhart, C.G. (2006). Notch3 signaling initiates choroid plexus tumor formation. *Oncogene*, Vol. 25, No.3, (January 2006), pp.487-491.

- Das, A., Tan, W.L, Teo, J., Smith, D.R. (2002). Expression of survivin in primary glioblastomas. *Journal of Cancer Research & Clinical Oncology*, Vol. 128, No.6, (January 2002), pp.302-6.
- Deuel, T. F., Zhang, N., Yeh, H. J., Silos-Santiago, I., Wang, Z. Y. (2002) Pleiotrophin: a cytokine with diverse functions and a novel signaling pathway. *Archives Biochemistry and Biophysics*, Vol.397, No. 2, (January 2002), pp. 162-167.
- Fabri, L., Maruta, H., Muramatsu, H., Muramatsu, T., Simpson, R. J. et al. (1993) Structural characterisation of native and recombinant forms of the neurotrophic cytokine MK. *The Journal of Chromatography*, Vol.646, No.1 (August 1993), pp. 213-225.
- Fan, X., Mikolaenko, I., Elhassan, I., Ni, X., Wang, Y. et al. (2004). Notch1 and notch2 have opposite effects on embryonal brain tumor growth. *Cancer Research*, Vol. 64, No.21, (November 2004), pp.7787-7793.
- Furnari, F.B, Fenton, T., Bachoo, R.M, Mukasa, A., Stommel, J.M et al. (2007). Malignant astrocytic glioma: genetics, biology, and paths to treatment. *Genes Development*, Vol.21, No. 21, (November 2007), pp.2683-710.
- Grzelinski, M., Steinberg, F., Martens, T., Czubyko, F., Lamszus, K. et al. (2009). Enhanced antitumorigenic effects in glioblastoma on double targeting of pleiotrophin and its receptor ALK. *Neoplasia*, Vol.11, No.2, (February 2009), pp.145-56.
- Gustavsson, H., Jennbacken, K., Welén, K., Damber, J.E. (2008). Altered expression of genes regulating angiogenesis in experimental androgen-independent prostate cancer. *Prostate*, Vol.68, No.2, (February 2008), pp.161-70.
- Hu, R., Yan, Y., Li, Q., Lin, Y., Jin, W. et al. (2010). Increased drug efflux along with midkine gene high expression in childhood B-lineage acutelymphoblastic leukemia cells. *International Journal of Hematology*, Vol. 92, No.1, (July 2010), pp.105-10.
- Huang, Y., Hoque, M. O., Wu, F., Trink, B., Sidransky, D. et al. (2008) Midkine induces epithelial-mesenchymal transition through Notch2/Jak2-Stat3 signaling in human keratinocytes. *Cell Cycle*, Vol.7, No.11, (June 2008), pp. 1613-1622.
- Huang, Y., Sook-Kim, M. and Ratovitski, E. (2008) Midkine promotes tetraspanin-integrin interaction and induces FAK-Stat1a pathway contributing to migration/invasiveness of human head and neck squamous cell carcinoma cells. *Biochemical and Biophysical Research Communications*, Vol.377, No.2, (December 2008), pp. 474-478.
- Huang, Z., Cheng, L., Guryanova, O.A., Wu, Q., Bao, S. (2010). Cancer stem cells in glioblastoma-molecular signaling and therapeutic targeting. *Protein and Cell*, Vol.1, No.7, (July 2010), pp.638-55.
- Hussain, M.M., Strickland, D.K., Bakillah, A. (1999). The mammalian low-density lipoprotein receptor family. *The Annual Review of Nutrition*. Vol.19, pp.141-172.
- Ichihara-Tanaka, K., Oohira, A., Rumsby, M. And Muramatsu, T. (2006) Neuroglycan C is a novel midkine receptor involved in process elongation of oligodendroglial precursor-like cells. *The Journal of Biological Chemistry*, Vol.281, No. 41, (October 2006), pp.30857-30864.

- Ikushima, H., Todo, T., Ino, Y., Takahashi, M., Miyazawa, K. et al. (2009). Autocrine TGF-beta signaling maintains tumorigenicity of glioma-initiating cells through Sry-related HMG-box factors. *Cell Stem Cell*, Vol. 5, No. 5, (November 2009), pp. 504-514.
- Iwasaki, W., Nagata, K., Hatanaka, H., Inui, T., Kimura, T. et al. (1997) Solution structure of midkine, a new heparin-binding growth factor. *The EMBO Journal*, Vol. 16, No. 23, (December 1997), pp. 6936-6946.
- Kadomatsu K. (2010). Midkine regulation of the renin-angiotensin system. *Current Hypertension Reports*, Vol. 12, No. 2, (April 2010), pp. 74-9.
- Kadomatsu, K., Huang, R.-P., Suganuma, T., Murata, F., Muramatsu, T. (1990), A retinoic acid responsive gene MK found in the teratocarcinoma system is expressed in spatially and temporally controlled manner during mouse embryogenesis. *The Journal of Cell Biology*, Vol. 110, No. 3, (March 1990), pp. 607-616
- Kajiwara, Y., Yamasaki, F., Hama, S., Yahara, K., Yoshioka, H. et al. (2003) Expression of survivin in astrocytic tumors: Correlation with malignant grade and prognosis. *Cancer*, Vol. 97, No. 4, (February 2003), pp. 1077-83.
- Kilpelainen, I., Kaksonen, M., Kinnunen, T., Avikainen, H., Fath, M. et al. (2000) Heparin binding growth-associated molecule contains two heparin-binding b-sheet domains that are homologous to the thrombospondin type I repeat. *Journal of Biological Chemistry*, Vol. 275, No. 18, (May 2000), pp. 13564-13570.
- Kemik, O., Sumer, A., Kemik, A.S., Hasirci, I., Purisa, S. et al. (2010). The relationship among acute-phase response proteins, cytokines and hormones in cachectic patients with colon cancer. *World Journal of Surgical Oncology*, Vol. 8, (September 2010), pp. 85.
- Kleinschmidt-DeMasters, B.K., Heinz, D., McCarthy, P.J., Bobak, J.B., Lillehei, K.O. et al. (2003) Survivin in glioblastomas: Protein and messenger RNA expression and comparison with telomerase levels. *Archives of Pathology & Laboratory Medicine*, Vol. 127, No. 7, (July 2003), pp. 826-33.
- Kojima, S., Inui, T., Muramatsu, H., Suzuki, Y., Kadomatsu, K. et al. (1997). Dimerization of midkine by tissue transglutaminase and its functional implication. *The Journal of Biochemistry*, Vol. 272, No. 14, (April 1997), pp. 9410-9416.
- Krakstad, C., Chekenya, M. (2010). Survival signalling and apoptosis resistance in glioblastomas: opportunities for targeted therapeutics, *Molecular Cancer*. Vol. 9, (June 2010), pp. 135.
- Krieger, M., Herz, J. (1994). Structures and functions of multiligand lipoprotein receptors: macrophage scavenger receptors and LDL receptor-related protein (LRP). *The Annual Review of Biochemistry*, Vol. 63, pp. 601-637.
- Kurosawa, N., Chen, G. Y., Kadomatsu, K., Ikematsu, S., Sakuma, S. et al. (2001). Glypican-2 binds to midkine: the role of glypican-2 in neuronal cell adhesion and neurite outgrowth. *Glycoconjugate Journal*, Vol. 18, No. 6, (June 2001), pp. 499-507.
- Libermann, T.A., Nusbaum, H.R., Razon, N., Kris, R., Lax, I. et al. (1985a). Amplification, enhanced expression and possible rearrangement of EGF receptor gene in primary

- human brain tumours of glial origin. *Nature*, Vol. 313, No. 5998, (January 1985), pp.144-147.
- Libermann, T.A., Nusbaum, H.R., Razon, N., Kris, R., Lax, I. et al. (1985b). Amplification and overexpression of the EGF receptor gene in primary human glioblastomas. *Journal of Cell Science Supplement*, Vol.3, pp.161-172.
- Lino, M.M, Merlo, A., Boulay, J.L.(2010). Notch signaling in glioblastoma: a developmental drug target? *BMC Medicine*, Vol.8, (November 2010), pp.72.
- Lucas S., Henze G., Schnabel D., Barthlen W., Sakuma S. et al. (2010). Serum levels of Midkine in children and adolescents without malignant disease. *Pediatrics International*, Vol.52, No.1, (February 2010), pp.75-9.
- Ma, J., Meng, Y., Kwiatkowski, D.J., Chen, X., Peng, H. et al. (2010). Mammalian target of rapamycin regulates murine and human cell differentiation through STAT3/p63/Jagged/Notch cascade. *The Journal of Clinical Investigation*, Vol.120, No. 1, (January 2010), pp.103-114.
- Maeda, N., Ichihara-Tanaka, K., Kimura, T., Kadomatsu, K., Muramatsu, T. et al. (1999) A receptor-like protein-tyrosine phosphatase PTPz/ RPTPb binds a heparin-binding growth factor midkine. Involvement of arginine 78 of midkine in the high affinity binding to PTPz. *Journal of Biological Chemistry* Vol. 274, No. 18, (April 1999), pp.12474-12479.
- Maruyama, K., Muramatsu, H., Ishiguro, N., Muramatsu, T. (2004). Midkine, a heparin-binding growth factor, is fundamentally involved in the pathogenesis of rheumatoid arthritis. *Arthritis & Rheumatism*, Vol.50, No.5, (May 2004), pp.1420-9.
- Matsui, T., Ichihara-Tanaka, K., Lan, C., Muramatsu, H., Kondou, T. et al. (2010). Midkine inhibitors: application of a simple assay procedure to screening of inhibitory compounds. *International Archives of Medicine*, Vol.3, (June 2010), pp.12.
- Merlo, A. (2003). Genes and pathways driving glioblastomas in humans and murine disease models. *Neurosurgical Review*, Vol.26, (July 2003), pp.145-158.
- Mirkin, B.L., Clark, S., Zheng, X., Chu, F., White, B.D. et al. (2005). Identification of midkine as a mediator for intercellular transfer of drug resistance. *Oncogene*. Vol.24, No.31, (July 2005), pp.4965-74.
- Mishima, K., Asai, A., Kadomatsu, K., Ino, Y., Nomura, K., et al. (1997). Increased expression of midkine during the progression of human astrocytomas. *Neuroscience Letters*, Vol 233, No.1, (September 1997), pp.29-32.
- Mitsiadis, T.A., Salmivirta, M., Muramatsu, T., Muramatsu, H., Rauvala, H., et al. (1995) Expression of the heparin-binding cytokines, midkine (MK) and HB-GAM (pleiotrophin) is associated with epithelial-mesenchymal interactions during fetal development and organogenesis. *Development*, Vol.121, No.1, (January 1995), pp. 37-51.
- Muramatsu, T. (2010). Midkine, a heparin-binding cytokine with multiple roles in development, repair and diseases. *Proceedings of the Japan Academy, Ser. B, Physical and Biological Sciences*, Vol. 86, No.4, pp. 410-425.

- Muramatsu, H., Zou, K., Sakaguchi, N., Ikematsu, S., Sakuma, S. et al. (2000) .LDL receptor-related protein as a component of the midkine receptor. *Biochemical and Biophysical Research Communication*, Vol. 270,(April 2000), pp. 936-941.
- Muramatsu, H., Inui, T., Kimura, T., Sakakibara, S., Song, XJ., et al. (1994) Localization of heparin-binding, neurite outgrowth and antigenic regions in midkine molecule. *Biochemical and Biophysical Research Communications*, Vol. 203,(September 1994), pp.1131-1139.
- Muramatsu, H., Zou, P., Suzuki, H., Oda, Y., Chen, G. Y., et al. (2004) .a4b1- and a6b1-integrins are functional receptors for midkine, a heparin-binding growth factor. *Journal of Cell Science*, Vol.117,(October 2004),pp.5405-5415.
- Muramatsu, H., Shirahama, H., Yonezawa, S., Maruta, H. and Muramatsu, T. (1993) Midkine, a retinoic acid-inducible growth/differentiation factor: immunochemical evidence for the function and distribution. *Developmental Biology*, Vol.159,(October 1993),pp. 392-402.
- Muramatsu, H., Zou, P., Kurosawa, N., Ichihara-Tanaka, K., Maruyama, K., et al. (2006) Female infertility in mice deficient in midkine and pleiotrophin, which form a distinct family of growth factors. *Genes to Cells* ,Vol.11,(December 2006),pp. 1405-1417.
- Nobata, S., Shinozawa, T., Sakanishi, A.(2005). Truncated midkine induces transformation of cultured cells and short latency of tumorigenesis in nude mice. *Cancer Letters*,Vol.219,No.1,(February 2005),pp. 83-9.
- Ohgaki, H., Dessen, P., Jourde, B., Horstmann, S., Nishikawa, T. et al.(2004).Genetic pathways to glioblastoma: a population-based study. *Cancer Research* ,Vol. 64, (October 2004), pp.6892-6899.
- Ohuchida, T., Okamoto, K., Akahane, K., Higure, A., Todoroki, H. et al. (2004) Midkine protects hepatocellular carcinoma cells against TRAILmediated apoptosis through down-regulation of caspase-3 activity. *Cancer*, Vol.100, (june 2004),pp.2430-2436.
- Ota, K., Fujimori, H., Ueda, M., Shiniriki, S., Kudo, M. Et al.(2008). Midkine as a prognostic biomarker in oral squamous cell carcinoma. *British Journal of Cancer*, Vol.99, No.4,(Augst 2008), pp. 655-62.
- Owada, K., Sanjo, N., Kobayashi, T., Mizusawa, H., Muramatsu, H. et al. (1999) Midkine inhibits caspase-dependent apoptosis via the activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase in cultured neurons. *Journal of Neurochemistry*, Vol.73,(November 1999),pp.2084-2092.
- Panchision, D.M.(2009).The role of oxygen in regulating neural stem cells in development and disease. *J Cell Physiol*,Vol.220,(September 2009), pp.562-568.
- Patten, BA., Sardi, SP., Koirala, S., Nakafuku, M., Corfas, G.(2006). Notch1 signaling regulates radial glia differentiation through multiple transcriptional mechanisms. *The Journal of Neuroscience*, Vol.26, (March 2006),pp.3102-3108.
- Powers, C., Aigner, A., Stoica, GE., McDonnell, K., Wellstein, A.(2002). Pleiotrophin signaling through anaplastic lymphoma kinase is rate-limiting for glioblastoma growth. *The Journal of Biological Chemistry*, Vol.277, No.16,(April 2002),pp.14153-8.

- Purow, B.W., Sundaresan, T.K., Burdick, M.J., Kefas, B.A., Comeau, L.D. et al.(2008).Notch-1 regulates transcription of the epidermal growth factor receptor through p53. *Carcinogenesis*, Vol. 29,(May 2008), pp.918-925.
- Rauvala, H., Peng, H.B. (1997). HB-GAM (heparin-binding growth-associated molecule) and heparin-type glycans in the development and plasticity of neuron-target contacts. *Progress in Neurobiology*,Vol 52, (June 1997),pp.127-144.
- Rawnaq, T., Kunkel, M., Bachmann, K., Simon, R., Zander, H. et al.(2010). Serum Midkine Correlates with Tumor Progression and Imatinib Response in Gastrointestinal Stromal Tumors. *Annals of Surgical Oncology*, (Jun 2010) , [Epub ahead of print] PubMed.
- Rosenbaum, C., Röhrs, S., Müller, O., Waldmann, H. Modulation of MRP-1-mediated multidrug resistance by indomethacin analogues. (2005).*Journal of Medicinal Chemistry*,Vol.48, No.4,( February 2005), pp.1179-87.
- Qin, Li, L., Lian Huang, H., Liang Ping, J., Xu, W., Li, J. et al.(2011). Expression of midkine and endoglin in breast carcinomas with different immunohistochemical profiles. *Acta Pathologica, Microbiologica et Immunologica Scandinavica*, Vol.119,No.2, (February 2011), pp.103-10.
- Quant, E.C., Wen P.Y.(2010). Novel medical therapeutics in glioblastomas, including targeted molecular therapies, current and future clinical trials, *Neuroimaging Clinics North America*. Vol.20, No.3, (August 2010),pp.425-448.
- Sakamoto, K., Bu, G., Chen, S., Takei, Y., Hibi, K. et al.(2011),The premature ligand-receptor interaction during biosynthesis limits the production of growth factor midkine and its receptor LDL receptor-related protein 1(LRP1).*The Journal of Biological Chemistry* (January 2011 ) [Epub ahead of print]
- Sato, W., Kadomatsu, K., Yuzawa, Y., Muramatsu, H., Hotta, N. et al. (2001) Midkine is involved in neutrophil infiltration into the tubulointerstitium in ischemic renal injury. *The Journal of Immunology*. Vol.167, (September 2001),pp.3463-3469.
- Satoh, H., Muramatsu, G., Moretto, T., Muramatsu, H.J., Chang, ST. et al. (1993). Midkine that promotes survival of fetal human neurons is produced by fetal human astrocytes in culture. *Brain Research*,Vol. 75 , pp. 201-205.
- Shibata, Y., Muramatsu T., Hirai M., Inui, T., Kimura, T. et al. (2002).Nuclear targeting by the growth factor midkine. *Molecular and Cellular Biology*,Vol.22,No.19,(October 2002),pp.6788-96.
- Sivasankaran, B., Degen, M., Ghaffari, A., Hegi, M.E., Hamou, M.F. et al.(2009).Tenascin-C is a novel RBPJk-induced target gene for Notch signaling in gliomas. *Cancer Research*,Vol. 69,(January 2009),pp.458-465.
- Solecki, D.J., Liu, X.L., Tomoda, T., Fang, Y., Hatten, M.E. (2001). Activated Notch2 signaling inhibits differentiation of cerebellar granule neuron precursors by maintaining proliferation. *Neuron*, Vol.31,(August 2001), pp.557-568.
- Stoica, G E., Kuo, A., Powers, C., Bowden, E T., Sale, E B. et al. (2002) Midkine binds to anaplastic lymphoma kinase (ALK) and acts as a growth factor for different cell types. *The Journal of Biological Chemistry*, Vol. 277, (September 2002), pp.35990-35998.

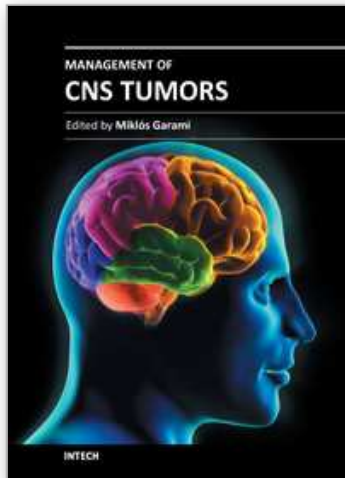
- Mitsiadis, T.A., Salmivirta, T., Muramatsu, H., Muramatsu, H., Rauvala, E. et al. (1995). Thesleff, Expression of the heparin-binding cytokines, midkine (MK) and HB-GAM (pleiotrophin) is associated with epithelial-mesenchymal interactions during fetal development and organogenesis. *Development*, Vol.121, (January 1995), pp. 37-51.
- Takei, Y., Kadomatsu, K., Matsuo, S., Itoh, H., Nakazawa, K. et al. (2001). Antisense oligodeoxynucleotide targeted to Midkine, a heparinbinding growth factor, suppresses tumorigenicity of mouse rectal carcinoma cells. *Cancer Research*, Vol. 61, (December 2001), pp.8486-8491.
- Takei, Y., Kadomatsu, K., Goto, T., Muramatsu, T. (2006). Combinational antitumor effect of siRNA against midkine and paclitaxel on growth of human prostate cancer xenografts. *Cancer*, Vol.107, No.4,(August 2006), pp.864-73.
- Take, M., Tsutsui, J., Obama, H., Ozawa, M., Nakayama, T. et al. (1994). Identification of nucleolin as a binding protein for midkine (MK) and heparin-binding growth associated molecule (HB-GAM). *The Journal of Biochemistry*, Vol.116,(November 1994), pp.1063-1068.
- Tanaka M, Kadokawa Y, Hamada Y, Marunouchi T (1999) Notch2 expression negatively correlates with glial differentiation in the postnatal mouse brain. *J Neurobiol*, Vol. 41, No. 4 (December 1999), pp. 524-539.
- Ulasov, IV., Rivera, AA., Sonabend, AM., Rivera, LB., Wang, M. et al. (2007). Comparative evaluation of survivin, midkine and CXCR4 promoters for transcriptional targeting of glioma gene therapy. *Cancer Biology & Therapy*, Vol.6, No.5, (May 2007), pp. 679-85.
- Wang, J., Takeuchi, H., Sonobe, Y., Jin, S., Mizuno, T. et al. (2008). Inhibition of midkine alleviates experimental autoimmune encephalomyelitis through the expansion of regulatory T cell population. *Proceedings of the National Academy Sciences online U S A*, Vol.105, No. 10, (March 2008), pp.3915-20.
- Wang, J., Takeuchi, H., Sonobe, Y., Jin, S., Mizuno, T. et al. (2008). Inhibition of midkine alleviates experimental autoimmune encephalomyelitis through the expansion of regulatory T cell population. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.105, No.10,(March 2008), pp.3915-20.
- Yamada, Y., Kuroiwa, T., Nakagawa, T., Kajimoto, Y., Dohi, T. et al. (2003) Transcriptional expression of survivin and its splice variants in brain tumors in humans. *Journal of Neurosurgery* Vol.99, No. (October 2003), pp.738-45.
- Yang, L., Cao, Z., Li, F., Post, DE., Van Meir, E.G. et al. (2004) Tumor-specific gene expression using the survivin promoter is further increased by hypoxia. *Gene Therapy*, Vol. 11, No.15, (August 2004), pp.1215-23.
- Yao, X., Tan, Z., Gu, B., Wu, R.R., Liu, Y.K. et al. (2010). Promotion of self-renewal of embryonic stem cells by midkine. *Acta Pharmacologica Sinica*, Vol.31, No.5,(May 2010), pp.629-37.



- Zou, K., Muramatsu, H., Ikematsu, S., Sakuma, S., Salama, RH. et al. (2000). A heparin-binding growth factor, midkine, binds to a chondroitin sulfate proteoglycan, PG-M/versican. *European Journal of Biochemistry*, Vol. 267, (July 2000), pp.4046-4053.
- Zou, P., Muramatsu, H., Miyata, T., Muramatsu, T. (2006). Midkine, a heparin-binding growth factor, is expressed in neural precursor cells and promotes their growth. *Journal of Neurochemistry*, Vol.99, No.6, (December 2006), pp.1470-9.

IntechOpen

IntechOpen



## **Management of CNS Tumors**

Edited by Dr. Miklos Garami

ISBN 978-953-307-646-1

Hard cover, 464 pages

**Publisher** InTech

**Published online** 22, September, 2011

**Published in print edition** September, 2011

Management of CNS Tumors is a selected review of Central Nervous System (CNS) tumors with particular emphasis on pathological classification and complex treatment algorithms for each common tumor type. Additional detailed information is provided on selected CNS tumor associated disorders.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Ayhan Bilir and Mine Erguven (2011). Midkine Signaling in Glioblastoma: A Novel Developmental Drug Target?, Management of CNS Tumors, Dr. Miklos Garami (Ed.), ISBN: 978-953-307-646-1, InTech, Available from: <http://www.intechopen.com/books/management-of-cns-tumors/midkine-signaling-in-glioblastoma-a-novel-developmental-drug-target->

# **INTECH**

open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](#), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen