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Midkine Signaling in Glioblastoma: A Novel Developmental Drug Target?

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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 suffred 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, prospensity for necrosis, robust angiogenesis, high resistance to apoptosis, and genomic instability. The intratumoral heterogenity 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 (progessive) 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 supressor 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 supressor genes [p53, phosphatase and tensin homolog deleted on choromosome 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) amplications 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 supressors p53, Rb, PTEN (~10 %), loss of chromosomes 10q, 11p, 19q, (2) amplications 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 thrompospondin 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 β-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 activiy. 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), α4β1-integrin and α6β1-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 a6b1-integrin and tetraspanin, and induces tyrosine phosphorylation of focal adhesion kinase (FAK) followed by activation of paxillin and **s**ignal **t**ransducer and **a**ctivator of **t**ranscription alpha (STAT1α) 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-κB) (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 β/ς 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 β/ς 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-1α) and consequently promotes differentiation or apoptosis, HIF-1α 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 (Ulusov 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 complexicity 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 **trans**activates 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 occured when a subset of cells overexpress drug transport proteins, possess receptor changes for the commitment of drug bounding 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 hypothized 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 supression 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 72nd 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 occured 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-(trifluoromethy)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 supresion 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 metioned 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 antiphysciotic 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 result 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 Nos 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. Complexicity of GBM can be seen basicly 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

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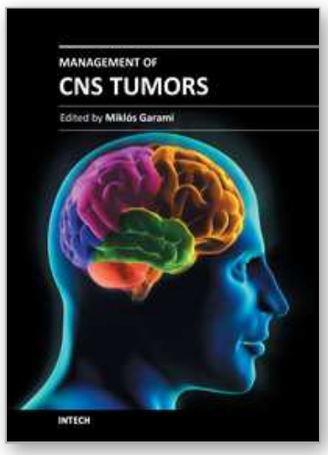

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