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Molecular Targets: Inhibition of Tumor Cell Invasion

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1. Introduction

Gliomas are solid brain tumors that arise from glial cells. According to World Health Organization (WHO), they are classified in four grades based in their histological features. Grades I and II are considered low-grade gliomas and grades III and IV, malignant gliomas. In the United States, each year more than 22,000 people are diagnosed with malignant glioma, representing almost 70% of all malignant primary brain tumors in adults (Wen & Kesari, 2008; CBTRUS 2010; Jones & Holland, 2010).

Despite years of research, mortality rates are still high for patients diagnosed with malignant gliomas. Glioblastoma multiforme (WHO grade IV) is the most frequent malignant brain tumor in adults. Even with heavy treatment that includes surgery, radiotherapy and adjuvant chemotherapy, the median survival remains in the range of 12-15 months for patients with this type of tumor (Minniti et al., 2009; Jones & Holland, 2010).

Glioblastomas are separated in two main subtypes: primary glioblastomas and secondary glioblastomas. Primary glioblastoma affects preferentially patients older than 50 years old and has genetic alterations as epidermal growth factor receptor (EGFR) amplification and mutation, loss of heterozygosity of chromosome 10q, deletion of the phosphatase and tensin homologue on chromosome 10 (PTEN), and p16 deletion. Secondary glioblastoma starts as low-grade or anaplastic astrocytomas in younger patients and progresses to glioblastoma over the years. Its main alterations involve mutations in *TP53*, overexpression of platelet derived growth factor receptor (PDGFR), changes in p16 and retinoblastoma pathways, and loss of heterozygosity of chromosome 10q. Even morphologically similar, primary and secondary glioblastomas may differ in their response to molecular targeted therapy (Wen & Kesari, 2008).

1.1 Current treatment

Choosing the best treatment depends on the type of tumor, position in the brain, its size and its grade. For patients newly diagnosed with brain malignancies, the current standard treatment protocols include maximally surgical resection, followed by chemotherapy concomitant to fractioned radiation therapy of the tumor. Adjuvant chemotherapy for

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glioblastomas is based on alkylating agents-based as temozolomide (TMZ) or carmusite wafers (Gliadel®), the latter being inserted in the surgery cavity during operation (Argyriou et al., 2009; Minniti et al., 2009). TMZ is a second-generation imidazotetrazine derivative and its cytotoxic effects are caused by the methylation of specific DNA site as O_6 position of guanine. In recurrent tumors some patients undergo reoperation. The chemotherapy used in this case is carmusite wafers (Gliadel®), conventional therapy as lomusite, PCV and carboplatin, bevacizumab plus irinotecan, and experimental therapies (Wen & Kesari, 2008). Although these treatments are well established, they are still just palliative and not curative in almost all cases.

The failure in malignant glioma treatment is due multiple causes that include invasive nature of glioma cells, resistance to radiotherapy and chemotherapy; and presence of the blood brain barrier (Figure 1).

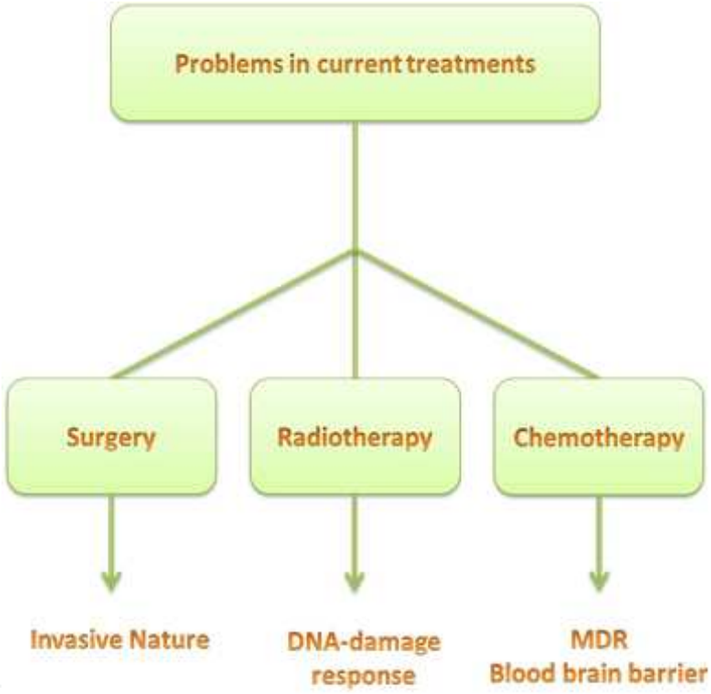

Fig. 1. Causes of resistance to current treatments. MDR = multidrug resistance.

1.2 Resistance

Resistance is a current problem in the treatment of almost all cancers, and in glioma this would not be different. Malignant gliomas have some characteristics that make them especially difficult to treat. Due to the diffuse nature of gliomas, they should not be considered a local disease. This feature limits the effectiveness of local therapeutic approaches, as surgery (Goldbrunner et al., 1999). Other important factors are the presence of the blood brain barrier (BBB) and the inter- and intratumor heterogeneity which lead to fail in radio and chemotherapies (Jones & Holland).

Combination of chemotherapy with radiation has improved a little the patient survival. However, these results are still very far from providing an effective treatment. Multidrug

resistance (MDR) is one of the reasons for the poor response to standard treatments. MDR is a characteristic of cancer cells where these cells are resistant to an abroad spectrum of drugs with different modes of action. The mechanisms of chemoresistance are complex and multifactorial; and can be separated in intrinsic resistance or acquired resistance. The intrinsic resistance is present at the beginning of the treatment. The drug-resistant cells already express one or more resistance-mediating proteins or pathways. The acquired resistance is the resistance that is developed during the treatment. The three major mechanisms of drug resistance in cells are related to decreased uptake, especially for drugs that need transporters to enter the cell; changes in the cell regarding cell cycle, DNA-damage repair, apoptosis and drug metabolism, leading to alteration in the cytotoxicity of some drugs; and increase in the energy demanding to hydrophobic drugs to enter the cell caused by the activity of drug pumps as the ATP-binding cassette (ABC) transporters (Szakács et al., 2006; Lage, 2008; Lu & Shervington, 2008).

An important type of cell involved in malignant glioma resistance is the cancer stem cell. Although stem cells represent just a small part of the cells within malignant gliomas, it seems that they have an important role in the resistance to standard treatments, being radioresistant and chemoresistant (Adamson et al., 2009; Huang et al., 2010; Huse & Holland, 2010; Lamszus & Günther, 2010). Cancer stem cells are more resistant to radiation when compared to non-stem glioma cells. Radioresistance is due to the activation of pathways involved in DNA damage checkpoint response, leading to a more efficient DNA damage repair and a more rapidly recover from genotoxic stress. Radiotherapy affects tumor cells preferentially through DNA damage. For that reason, damage checkpoint responses are essential to radiosensitivity in cells. Chemoresistance in stem cells is probably caused by enhanced expression of BCRP1 and *O6*-methylguanine-DNA-methyltransferase (MGMT) as well as anti-apoptosis proteins. The ABC transporter BCRP1 has been playing an important role in drug resistance of normal and tumor stem cells while the presence of MGMT which is a DNA repair protein protects tumor cells against alkylating chemotherapeutic agents, such as TMZ (Bao et al., 2006; Liu et al., 2006; Wen & Kesari, 2008; Van Meir et al., 2010).

The use of chemotherapy is also limited due to the presence of the blood brain barrier (BBB). It restricts the action of conventional drugs that have difficulty to reach their therapeutic concentrations into the tumor and peritumor area. Only highly hydrophobic and low-molecular weight molecules are able to penetrate into the brain and reach their targets. There have been several attempts to improve drug delivery and increase its local concentration as intra-arterial delivery or opening the BBB using analogs of bradykinin (RMP-7). However, none has shown great result (Giese et al, 2003; Argyriou et al., 2009).

Apart from mechanisms of resistance described above, most of the treatments fail because of the highly invasive nature of glioma cells. Groups of cells or single cells can detach from the main tumor mass and invade long distances. The capacity of glioma cells to penetrate within the normal brain brings great clinical challenges because the remaining cells are believed to be responsible for tumor recurrence after standard treatments. The image methods available are not able to track these cells and it is not known the proportion of migratory cells affected by the current therapy (Berens & Giese, 1999; Claes et al., 2007). Another challenge in targeting the remaining cells is redundancy in the signaling pathways that lead to cell motility. Nowadays there are a lot of studies involving targets that are unique of brain ECM,

cell surface receptors, and signaling molecules activated in migrating cells. These include tenascin C, brevican, Src family of non receptor tyrosine kinases, Rho family of small GTPases, glycogen synthase kinase 3 (GSK-3), and integrins. The highly complex pro-migratory signaling, the influence of microenvironment, and the unique nature of the invasive process in the brain provide an extensive area of study for the next years (Van Mer et al., 2010). This review focuses on the mechanisms involved in glioma cell migration and the potential molecular targets within these pathways.

2. Glioma invasion and microenvironment

Invasion is a characteristic not exclusive for malignant gliomas. Low-grade astrocytomas can also show extensive infiltration of normal brain, limiting resection and eventually leading to recurrence and progression of the disease. However, the dynamic of high-grade glioma invasion seems to be more rapid (Giese et al., 2003; Louis, 2006; Jones & Holland, 2010). Although this type of tumor is extremely invasive, metastasis out of the brain is rare. Invasive cells tend to follow existing anatomical structures, and migrate along myelinated fiber tracts as corpus callosum, meninges and the ventricular lining and the perivascular regions (Tysnes & Mahesparan, 2001).

The invasive nature of glioma cells is one of the major problems of this type of cancer. After resection of the main tumor, the residual pool of invasive cells gives rise to recurrent tumor. Interaction between cells and extracellular matrix (ECM) is the main factor to maintain the normal features of tissues. The loss of ECM control is a hallmark in tumor progression toward invasion. Although brain tumor cells share common invasive characteristics with other tumor cell types, the different composition of the brain ECM suggests alternative invasive mechanisms for brain tumor cells. This unique brain ECM composition may also be one of the reasons for the poorly metastatic behavior even though the cells are highly invasive (Tysnes & Mahesparan, 2001). The human brain ECM consists mainly of glycosaminoglycans (GAGs) and proteoglycans. The four main GAGs are hyaluronic acid, chondroitin sulfate, keratin sulfate and heparin sulfate. The presence of glycoproteins as fibronectin or collagen, are limited. The interaction between GAG hyaluron and the other GAGs or glycoproteins forms a loose ECM-meshwork around axons, neurons, and glial cells of the white and gray matter (Goldbrunner et al., 1998).

Invasion is a complex and dynamic process that has three basic coordinated steps: adhesion to the ECM, cytoskeleton rearrangement, and degradation of ECM components (Figure 2). Cells have to interact with their microenvironment to be able to migrate and invade. Integrins together with CD44 receptor are the receptors responsible for glioma cells-ECM adhesions. Migrating cells interact with ECM components forming transition adhesions which will have two main functions: generate signals that lead to cytoskeletal rearrangement and support cell traction. Cells also need space to migrate and ECM proteolysis is accomplished by activation of several proteases such as matrix metalloproteinases (MMPs) and plasmin secreted by glioma cells and endothelial cells. Cytoskeletal rearrangements lead to cell polarization and formation of membrane protrusion for which RhoGTPase family plays a major role. Cells invade by actively migrating into the newly created space (Goldbrunner et al., 1999; Bellail et al., 2004; Teodorczyk & Martin-Villalba, 2010).

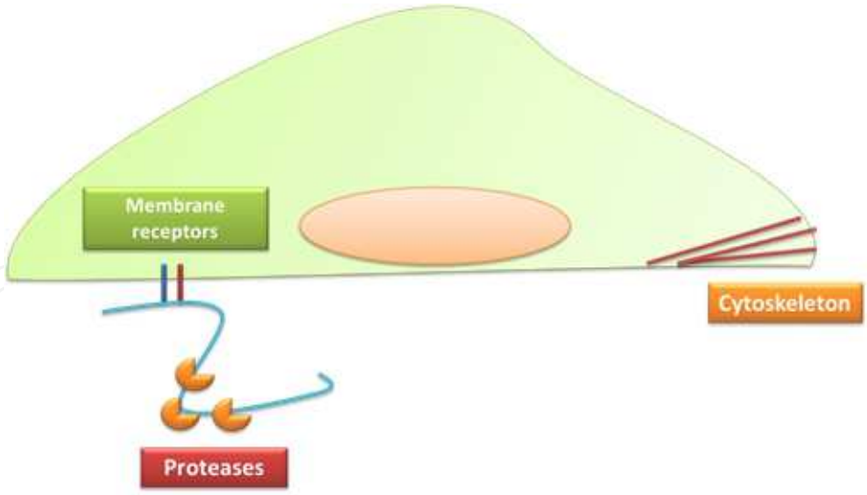

Fig. 2. The three components related to the invasion process. Membrane receptors as integrins and CD44 receptor are responsible for the cell-ECM interaction. Actin filaments are important cytoskeleton structures that rearrange to allow cell to migrate. Proteases as matrix metalloproteinases (MMPs) degrade ECM components and open space to cell migration.

2.1 ECM components

It is known that some ECM components are upregulated within tumor stroma and within brain parenchyma surrounding tumor area. Among them are hyaluronan, vitronectin, osteopontin, tenascin-C, SPARC and BEHAB (Bellail et al., 2004).

Hyaluronan (HA) is a glycosaminoglycan and the major component of brain ECM. In normal ECM, HA is responsible for tissue homeostasis, biomechanical integrity, and tissue structure. However, in malignant tumor tissue, it has been shown that HA facilitates primary brain tumor invasion *in vivo* and migration *in vitro* through its two receptors, CD44 and receptor for hyaluronan-mediatd motility (RHAMM) (Bellail et al., 2004; Park et al., 2008). The mechanisms of action are not completely elucidated but there are some evidences showing that HA induces tumor progression through pathways as PI3K/Akt/mTor/osteopontin and RhoGTPase signaling (Kim et al., 2005; Bourguignon, 2008).

Tenascin-C is a large modular glycoprotein. Tenascin-C signaling is mediated by integrin β1 via phosphorylation of focal adhesion kinase (FAK). It has been shown that tenascin-C is overexpressed in invasive glioma *in vivo* (Demuth & Berens, 2004).

BEHAB (brain-enriched hyaluronan-binding) protein, also known as brevican, is a chondroitin sulfate lectican. Its expression in the brain is very low being up-regulated in malignant gliomas. Its high expression and cleavage promote glioma invasion. Cleavage of BEHAB is mediated by metalloproteases of ADAMTs family (Gladson, 1999; Bellail et al., 2004; Viapiano et al., 2008).

2.2 Interaction with the ECM

Integrins are a family of transmembrane glycoprotein receptors. They are heterodimers and consist of α and β subunits non-covalently associated. To date there have been described 18

α subunits and 8 β subunits combining to form 24 integrins that bind to different ECM components. Some integrins are ubiquitously expressed while others depend on the tissue or stage of development (Brakebusch & Fässler, 2003; Berrier & Yamada, 2007). The interaction between integrins and ECM components activates a number of signaling pathways that control proliferation, differentiation, migration, and cell survival. Changes in both integrin and ECM molecules expression may cause important cell modifications contributing to malignant progression (Gladson, 1999).

Integrins are the main connection between ECM and cytoskeleton. When integrin binds its ligands, actin filaments and signaling proteins move to integrin´s cytoplasmic domain and form focal complexes. These complexes can grow in size and stabilize to form focal contacts or remain as focal complexes. Focal contacts are more mature and stable adhesions, usually found in the end of actin bundle called stress fibers. Focal complexes are less persistent cellular structures and suffer rapid turnover (Schoenwaelder & Burridge, 1999; Brakebusch & Fässler, 2003; Demuth & Berens, 2004).

Within Central Nervous System it has been described the presence of at least three integrin subunits. Subunits β_1 and α_v are described in a variety of cell types including neurons, glia cells, meningeal cells and endothelial cells. It has been reported differences in integrin expression in glioma cells. Subunits β_1 and α_3 are higher expressed in glioma cells when compared with normal cells and β_1 is being considered a key factor in glioma cell migration (Paulus & Tonn, 1994; Bellail et al., 2004; D´Abaco & Kaye, 2007).

CD44 receptor binds hyaluronic acid, one of the main brain ECM components. It is expressed in a variety of cells, including glial cells. Alternative mRNA splicing form several isoforms of CD44, being isoform CD44H the most important in normal brain as well as in primary brain tumor, including glioblastomas (Goldbrunner et al., 1998).

CD44 functions as both receptor and signaling molecule to induce cell migration and invasion through activation of actin reorganization pathways. As receptor, CD44 binds to HA and activates pathways described above. In tumor cells, CD44 is proteolytically cleavage at the extracellular domain by MMPs and CD44 cleavage is also important for CD44-mediated tumor cell migration. Engagement of CD44 augments CD44 cleavage by Rac activation (Murai et al., 2004; Teodorczyk & Martin-Villalba, 2010).

2.3 ECM proteolysis

Proteases are enzymes that cleave ECM components. They are secreted by glioma cells and seem to play an important role in cell migration. The most studied proteases are matrix metalloproteinases (MMPs) and the serine protease urokinase-type plasminogen activator (uPA) and its receptor. The role of these enzymes in glioma invasion is complex, since low-grade glioma invades the surrounding normal brain, even with normal level of the proteases (Louis, 2006; Drappatz et al., 2009).

MMPs are a family of zinc-dependent proteases. They are generally classified in four groups: collagenases, gelatinases, membrane-type MMPs (MT-MMPs) and stromelysins. The mechanisms that control MMP expression are not completely clear but some studies showed that MMPs can be regulated by ECM components, growth factors and cytokines. All MMPs are secreted as inactive proenzymes that need proteolytic cleavage for activation. The

proteolytic effect of MMPs is balanced by MMPs inhibitors as tissue-derived inhibitors of metalloproteinases (TIMPs). TIMPs bind to the active zinc-binding site of the MMP protein, forming an inactive complex. In malignant gliomas, there is an imbalance between expression of MMPs and their corresponding inhibitors which leads to a higher activity of MMPs and consequently greater ECM proteolysis (Newton, 2004).

uPA is secreted as a soluble protein and binds to its receptor (uPAR), a GPI-anchored protein. uPA is often up-regulated in malignant brain tumors and its activity is high at the edge of these tumors. Binding between this protease and its receptor is necessary for the activation of plasmin which can degrade ECM components. In 2003, Chandrasekar et al. reported that downregulation of uPA could inhibit glioblastoma cell migration and PI3K/Akt signaling *in vitro*. These results show the important role of uPA in glioma cell migration.

2.4 Cytoskeleton rearrangement

Directional cell migration undergoes a series of cytoskeletal reorganizations to create a leading edge and a trailing edge. At the leading edge there is the formation of membrane protrusions and the establishment of new matrix contacts, while at the trailing edge cell adhesions are disassembled to allow cells to move forward. Active remodeling of actin cytoskeleton is required to form structures at the front of the cell such as filopodia and lamellipodia. These structures have several actin filaments (F-actin) that are polymerized or depolymerized by the addition of G-actin at their barbed end or the release of G-actin at their pointed end. Cytoskeleton rearrangement depends on complex signaling pathways and is controlled mainly by the activation/deactivation of proteins from the Rho family of small GTPases (Berrier & Yamada, 2007; Wehrle-Haller & Imhof, 2003).

The Rho family of small GTPases has more than 20 members, including the well known proteins Cdc42, Rac and Rho. These proteins, as all small GTPases, cycle between an active GTP-bound and an inactive GDP-bound state. The activation and deactivation of Rho proteins are mediated by guanine nucleotide-exchange factors (GEFs) and GTPase-activating proteins (GAPs), respectively. There have been more than 70 RhoGTPase effector proteins described. The temporal and spatial balance between the different RhoGTPses are very important for the cellular processes. To promote cell migration, Rho protein activation is related to formation of focal adhesion complexes and stress fiber (bundle of actin filaments), while Rac and Cdc42 are associated with lamellipodia and filopodia formation, respectively (Iden & Collard, 2008).

2.5 Growth factors and other molecules

Overexpression of growth factor receptors and their ligands is very common in gliomas. Some growth factor receptors have been involved in glioma cell migration and invasion. Among these growth factor receptors are c-Met, epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR) (Gladson et al., 2010).

In particular, EGFR has been shown to be important for tumor growth and invasion (Tysnes & Mahesparan, 2001). Amplification and overexpression of EGFR are observed in 50% of glioblastoma multiforme. Malignant gliomas can also express a mutant receptor that is ligand independent, EGFRvIII. This receptor is constitutively phosphorylated and is more

tumorigenic than the wild-type receptor (Nakada et al., 2007). Activation of EGFR leads to signaling complex formation which initiates downstream signaling cascades, including the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK). These pathways regulate several cellular responses (Huang et al., 2009).

Platelet-derived growth factor (PDGF) is another growth factor that is upregulated in gliomas. Although PDGF is more related to proliferation and angiogenesis, some works have shown the influence of PDGF in cell motility in gliomas (Hoelzinger et al., 2007).

Transforming growth factor β (TGF-β) is present in tumor microenvironment and is secreted by malignant cells. This molecule can regulate cell motility, invasion, immune surveillance and angiogenesis. In glioblastoma multiforme, it has been reported the presence of TGF-β in tumor environment (Barcellos-Hoff et al., 2009; Drappatz et al., 2009).

Chemokines are small chemoattractant cytokines. These molecules and their receptors are expressed into the central nervous system by neurons and glia cells and are mediators of cell migration. In brain tumors their expression is deregulated. Special attention is given to CXCL12/CXCR4 axis because initial reports showed that CXCL12 promotes migration of glioma cells *in vitro* and activation of MMPs (Sciumè et al., 2010).

2.6 Intracellular signal

Interaction of glioma cells with their microenvironment leads to intracellular signals that are very complex and very integrated (Figure 3). When glioma cells receive a pro-invasive signal through cell-surface growth factor receptor and cell-adhesion receptor, signaling molecules are activated to amplify and propagate the message. The signaling molecules are represented by cytoplasmic tyrosine kinases, adaptor molecules, and cytoskeletal proteins (Gladson et al., 2010).

Growth factor receptor and cell-adhesion receptor signaling can be co-ordinated to control cell proliferation, survival and migration. It has been shown that integrins regulate some receptor tyrosine kinases (RTK) such as EGFR. This cross-talk can occur in at least three mechanisms: RTK activation, propagation of ligand-mediated signaling and synergetic interaction to reach a final biological response (Cabodi et al., 2004).

Focal adhesion kinase (FAK) is a downstream effector of integrins and growth factor receptors. The phosphorylation of FAK leads to the activation of several signaling pathways through protein phosphorylation and protein-protein interaction. FAK has different domains which allow the integration of different signaling pathways. Phosphorylated FAK activates several pathways, including PI3K/Akt, MAPK and $p130^{Cas}$/DOCK180/Rac. Overexpression of FAK is related with tumor progression (Schwock et al., 2010).

MAPK pathway – Activation of MAPK signaling pathway is triggered by growth factor receptor-bound-2 (Grb2)/son-of-sevenless (SOS) or FAK/Src complex. After RTK activation, autophosphorylation of the cytoplasmic domain of the receptor leads to recruitment of Grb2 and subsequently binding to the guanine exchange factor SOS. This complex interacts with small GTPase Ras and results in its activation. The next step is the sequential recruitment and activation of Raf, mitogen-activated protein kinase kinase (MEK) and extracellular signal-regulated kinase (ERK). ERK activates the expression of several transcriptional factors that control cell proliferation. Small GTPase Ras can also be activated by FAK/Src complex

when ECM components bind integrin. There is evidence that Src phosphorylates FAK, creating a binding site for the complex Grb2/SOS which leads to MAPK pathway activation (Giancotti & Ruoslahti, 1999; Ramos, 2008; Huang et al., 2009).

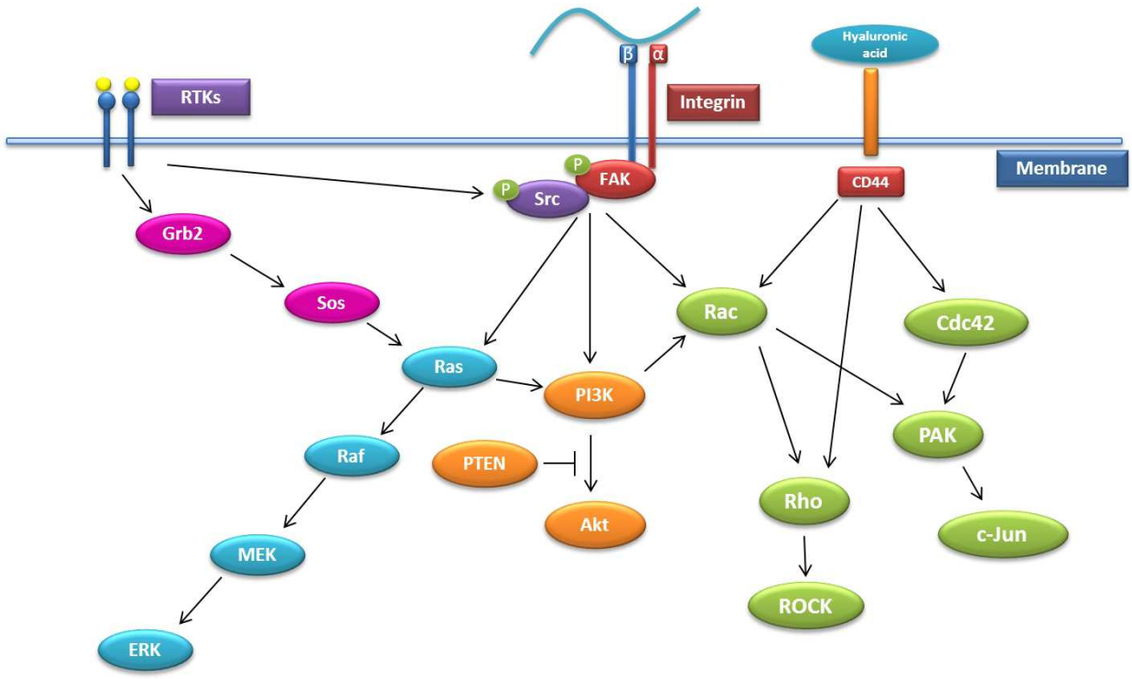

Fig. 3. Intracellular signal downstream cell-surface growth factor receptor and cell-adhesion receptor activation.

PI3K/Akt pathway – Activated PI3K converts plasma membrane phosphatidylinositol-4,5-bisphosphate (PIP_2) to phosphatidylinositol-3,4,5-triphosphate (PIP_3). PIP_3 leads to the activation of Akt that is involved in the regulation of several proteins related with cell survival. PI3K pathway is negatively regulated by phosphophoinositide phosphatases such as PTEN. PTEN acts in the opposite way of PI3K converting PIP_3 to PIP_2. Loss of PTEN leads to an imbalance of PI3K/PTEN and results in increased activation of PIP_3 and Akt (Huang et al., 2009).

ERK and Akt signaling cascades are related with proliferation and survival, respectively. However, they are also involved in the invasion process because the activation of these pathways leads to activation of MMPs as MMP-2 and MMP-9 (Park et al., 2008; Drappatz et al., 2009).

RhoGTPase pathway – Members of the Rho family of small GTPases (Rho-GTPases) are important intracellular mediators that control directional cell migration. They can be activated by several pathways, including integrin and CD44 signaling pathways. It is known that Rho-GTPases are implicated with metastasis and tumor progression, what is not so surprising since RhoGTPases are downstream pathways that are deregulated in several tumors. There are also evidences that some GEFs are up-regulated in malignant brain tumors which increase activation of RhoGTPases as Rac1 and RhoA. Rac1 and RhoA have been related to glioma cell migration and invasion (Salhia et al., 2006).

2.7 Epithelial-mesenchymal transition

Migrating cells need to detach from the tumor mass to infiltrate neighboring tissue. For that reason, other important process in glioma migration is the epithelial-mesenchymal transition (EMT). It consists on biochemical changes in polarized epithelial cells which allow the cell to assume a mesenchymal cell phenotype. This phenotype is characterized by enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and increased expression of ECM components (Kalluri & Weiberg, 2009). EMT is very important during embryogenesis but it is also present in pathological conditions such as tumorigenesis, hypoxia, and inflammation (Nieto, 2011). It is widely known that this process plays an important role in glioma migration. However, the molecules involved are still not well established.

Cadherins have an important role in EMT. Classically, expression of E-cadherin is reduced while expression of N-cadherin and cadherin-11 are increased during EMT. Nevertheless, E-cadherin expression is very low in normal brain tissue and some glioma cell lines (Lewis-Tuffin et al., 2010; Utsuki et al., 2002). The role of cadherins in gliomas is still obscure. Differences in the role of cadherins can change depending on the glioma cell line. E-cadherin is found in SF767 cells and its expression is related to more invasive phenotype. However, just N-cadherin and cadherin-11 are found in U87 cell line. Ectopic expression of E-cadherin did not show any affect in migration in the U87 cell line (Lewis-Tuffin et al., 2010).

Probably, acquisition of mesenchymal phenotype involves an E-cadherin-independent pathway in glioma. One possible candidate is the transcription factor TWIST1. Mikheeva et al., 2010 showed that TWIST1 is responsible for changes in glioma cells that correlate with the phenotype associated with carcinoma EMT.

3. Treatments involving molecular targets related to cell invasion

There are several characteristics that must be considered when choosing a therapeutic target. First of all, the target must be overexpressed in tumor cells but not in normal cells. The target must be active and contribute to the malignant phenotype. It is very important that the therapeutic agent reaches easily its pharmacological target. Usually the first approach is against secreted molecules and cell surface receptors (Rich & Bigner, 2004).

3.1 Drugs in clinical trials

Recent advances in the understanding of glioma biology and signaling pathways have provided new tools to the development of molecularly targeted agents. There are a wide variety of targeted agents being studied in preclinical and clinical trials. However, the use of these agents alone has shown limited efficacy in almost all studies. That way combined inhibition of multiple targets are being studying, using molecules against targets from the same pathway or targets of parallel pathways. Although this strategy has a great potential, it should be considered the increase in the risk of toxic effects (Clarke et al., 2010).

3.1.1 Integrins inhibitors

Integrins are highly express in gliomas. There are monoclonal antibodies and peptide-based integrin inhibitors being investigated against various tumor types. However, only

cilengitide (EMD121974 - Merck KGaA, Darmstadt, Germany) is being studied in glioma. Cilengitide is a synthetic Arg-Gly-Asp (RGD) pentapeptide that recognizes RGD ligand-binding motifs on integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$, blocking ligand binding. RGD is an important motif that is present in some ECM components (Hynes, 2002). Relevant responses have been observed with cilengitide monotherapy in preclinical and clinical studies. Some combinatorial studies were carried out adding cilengitide to standard radiotherapy/TMZ in a randomized phase II trial. The results showed promising efficacy, especially in patients with MGMT promoter methylation. Phase III trial (CENTRIC) has started recruiting newly diagnosed patients with methylated promoter of MGMT to assess efficacy and safety of cilengitide in combination with standard treatment against standard treatment (Khasraw & Lassman, 2010; Onishi et al., 2010; Tabatabai et al., 2010).

3.1.2 Anti-tenascin-C

Tenascin-C is overexpress in some patients with malignant gliomas and its presence seems to increase tumor cell invasion *in vitro* (Sarkar et al., 2006). Phase II studies using tenascin-specific antibody labeled with I^{131} (Neuradiab™) showed slight increase in survival time in patients with glioblastoma multiforme. Tenascin-specific antibody was administered directly into a surgically created resection cavity followed by standard treatment. Although some questions still remain, a Phase III trial of Neuradiab has started in patients with newly diagnosed glioblastoma multiforme (Akabani et al., 2005; Drappatz et al., 2009).

3.1.3 MMP inhibitors

Since the use of MMP inhibitors have shown decrease in glioma cell invasion *in vitro*, several clinical trials were performed. However, first and second generation of MMP inhibitors showed poor bioavailability and significant side effects. Marimastat is an orally drug that can reduce MMP levels in patients with glioma but several patients were remove from phase II trial because of intolerable side effects as join pain (Newton, 2004; Nakada et al., 2007; Onishi et al., 2011). New MMP inhibitors are in development to improve selectivity and to diminish side effects. A new class of MMP inhibitors targets the MMP S_1' subsite pocket and does not interact with the zinc active site. The MMP S_1' pocket has loop residues called S_1' specificity loop that vary in size and sequence depending on the MMP. Because of that these inhibitors are more selective. However, there are no current clinical trials (Overall & Kleifeld, 2006; Devel et al., 2010).

3.1.4 Anti-EGF receptor

Tyrosine kinase inhibitors avoid phosphorylation and activation of downstream signaling. The most studied molecules are erlotinib and gefitinib. They are reversible small-molecules inhibitors for oral use. Several Phase II clinical trials showed that monotherapy using erlotinib and gefitinib did not bring any significant survival benefit when compared to control group in patients with glioblastoma multiforme. Patients that co-expressed EGFRvIII and PTEN were more responsive to erlotinib. However, this result was not reproducible in another study, showing the high complexity of individual tumors. Combination of tyrosine kinase inhibitors with standard therapy did not show also good results. Recent clinical trials are evaluating other EGFR inhibitors as irreversible EGFR inhibitors BIBW 2992 and PF-

00299804 and the humanized monoclonal antibody against EGFR, nimotuzumab (Nakada et al., 2007; Hatanpaa et al., 2010; Van Meir et al., 2010)

3.2 Potential molecules in study

3.2.1 Lithium

Studies *in vitro* using lithium potently blocked glioma cell migration. This molecule is known to activate β-catenin signaling. The treatment had little effective in cell viability and was associated with change in cell morphology with retraction of long extensions at the leading edge, suggesting an involvement of glycogen synthase kinase (GSK-3). The role of GSK-3 in cancer cell migration is not clear but it was observed an inverse correlation between GSK-3 expression and rate of glioma invasion (Barcellos-Hoff et al., 2009).

3.2.2 Emodin

Emodin is one of the active components of the *Rheum palmatum* L. and is a protein tyrosine kinase inhibitor. It has several biological activity including antiviral, antimicrobial, immunosuppressive, and anticancer effects. Studies *in vitro* and *in vivo* showed that emodin decreased MMP-2 and MMP-9 expression by blocking FAK and Akt activation. It also suppressed HA-stimulated AP1 and NFκB promoter activities (Park et al., 2008).

3.2.3 RECK

RECK (Reversion-inducing-cysteine-rich protein with Kazal motifs) is a membrane-anchored glycoprotein. RECK can be found in various normal human tissues but its expression is low or undetectable in many tumors, including gliomas. RECK was first described as a tumor and metastasis suppressor gene, inhibiting at least three different metalloproteinases; MMP-2, MMP-9 and MT1-MMP. Re-expression of RECK in some tumor cell lines leads to a strong inhibition of tumor invasion, metastasis and angiogenesis (Takahashi et al., 1998; Oh et al., 2001; Noda et al., 2003; Meng et al., 2008). Corrêa et al. (2006) showed correlation between expression of RECK and invasive potential *in vitro*. The less invasive glioma cell line had higher RECK expression when compared to the more invasive glioma cell line.

In 2010, Corrêa et al. showed that overexpression of RECK in a glioma cell line (T98G) compromises glioma cell ability to migrate and invade *in vitro*. Results demonstrated that overexpression of RECK did not alter MMP activity but was responsible for cytoskeleton rearrangement, causing changes in cell motility. It is unknown how RECK leads to changes in cell motility but the elucidation of this mechanism could bring new potential targets to inhibit cell migration.

3.3 Issues in preclinical and clinical studies

In vitro experimental system and animal models are very important to study the biology of glioma invasion and to test anti-invasive therapy. They need to be accurate, representative and valid. Monolayer cultures of permanent glioma cell lines are widely used in experimental systems. However, these cell lines suffer biological changes during cell culture

and the lack of ECM-cell interaction causes changes in some gene expression, as shown by several studies (Nelson & Bissel, 2006). There are some 3D models available as spheroids but they also have some limitations because of the high complexity of tumors.

Brain tumor animal models are used to study new therapies. These models have to be accurate and reproducible to provide trustful results avoiding the exposure of patients to non-efficacious or unsafe drugs. Tumor xenografts models and transgenic models are two widely used animal models. These models have some advantages over *in vitro* models but they also have some limitations. For instance, xenografts models represent phenotypic diversity but they lack tumor environment interactions and do not reproduce invasive growth patterns. Transgenic models in the other way are good models for studying the impact of cell invasion, vascular limitations to drug delivery and interaction with the surrounding tissue. However, they do not reproduce tumor heterogeneity and genomic instability. For that reason, some drugs that have shown great anti-tumor activity fail in clinical trials (Rich & Bigner, 2004; King et al., 2005).

When studying a new drug, some parameters need to be evaluated: evaluation of dosing sequences, markers of therapeutic efficacy and intra-cerebral delivery. In clinical neuro-oncology trials there are some difficulties to measure efficacy and to obtain tumor tissue for sampling. Clinical efficacy should be based on overall survival. However, survival is not a good endpoint due to the variability of treatments that patients were submitted before and after trials. Biomarker measurement is essential to targeted therapy trials but lack of tissue sampling after experimental drug treatment is a problem (Rich & Bigner, 2004).

Chapter summary

- Failure in malignant glioma treatment is due multiple causes as local invasive nature of glioma cells, resistance to radiotherapy and chemotherapy; and presence of the blood brain barrier.
- Invasion is a major clinical problem. This process is highly complex, involving multiple pathways and relaying on a network of paracrine interactions. Contact between cells and the extracellular matrix is dynamic since it can change as cancer cells disseminate and reciprocally lead to activation of important signals for cytoskeleton rearrangement and matrix proteolyses.
- Treatment combining multiple drugs is the key to contain glioma progression, targeting not solely cancer cells but also the microenvironment. However, the discovery for new drugs is still a long process and improvement in models for preclinical tests is required.

4. Conclusion

Targeted therapy against invasion-related molecules is a promising alternative for treating malignant gliomas. Although tumor cells are widely disseminated when the patient is diagnosed, anti-invasive therapies for malignant gliomas have as its main goal to contain

the disease and increase the efficacy of local treatments. Migration signaling shares common pathways with proliferation and apoptosis. That way, the use of combining therapy could increase the efficient of conventional cytotoxic treatments, improving cell death. Advances in the understanding of tumor invasion have improved the development of new therapies. However, not all questions have been answered and some challenges still remain.

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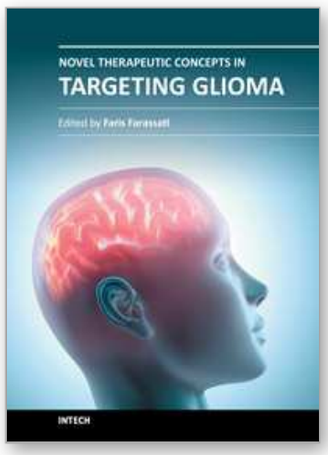

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