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Biomarkers of Glioma

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1. Introduction

According to the analysis of American Brain Tumor Association, the brain tumors are common with an incidence of 12.8 per 100,000 people. Glioma is the most common subgroup of brain tumors. It is a type of tumor that originates in the brain or spine. It is called a “glioma” because it arises from glial cells. According to the specific type of cells from which they originate, gliomas are categorized as glioblastoma (WHO grade IV), astrocytoma (WHO grades I-III), oligodendro-glioma (WHO grades II and III), and mixed glioma (WHO grades II and III) (McCarthy et al, 2011). It is reported that about 50% gliomas are glioblastomas, which are the most common and malignant phenotypic astrocytoma. They are most common in adults from ages 45-55, and affect more men than women. About 9% of brain tumors in childhood are glioblastomas.

Gliomas are difficult to treat. Usually the prognosis for patients with high-grade gliomas (especially for glioblastomas) is very poor, which has a mean survival only from 10 to 12 months (Reddy, et al, 2008). It is found that about 10,000 Americans are diagnosed annually with malignant gliomas, about half of these patients survive 1 year after diagnosis, and 25% after two years. The traditional approach to treat the glioma contains surgery, radiation therapy and chemotherapy. Although with these treatments or combined approaches, the tumor will be suppressed at some means, the survival rate of the patients is still very low.

Biomarker is a characteristic that is objectively measured as an indicator of normal biological processes, pathogenic processes or a pharmacological response to a therapeutic intervention (Atkinson et al., 2001; Marrer & Dieterle, 2007). And tumor/cancer biomarkers are involved in tumors which contain a wide variety of objects, including DNA, mRNA, secreted proteins, cell surface receptors, transcription factors, and metabolites, or processes such as apoptosis, angiogenesis or proliferation. The markers are produced either by the tumor itself or by other tissues or cells, in response to the presence of tumors or other associated irritation, like inflammation (Kulasingam & Diamandis, 2008). They can be found in the tumor tissues, tumor cell lines, secreted molecules and in the serum or other body fluid, and so on. The tumor/cancer biomarkers can help doctors to profile the cancer predisposition, state of cancerous development, early diagnosis, prognosis after treatment, and decide which drugs and at what dose it might be most effective to the patients with tumors. They are also beneficial to screen the targeted drug for the tumor treatment.

Recent years, the tumor/cancer biomarkers have played important roles in the diagnosis, therapy and prognosis in tumors. For example, prostate-specific antigen (PSA), as a best-

known cancer biomarker, is widely used to screen and diagnosis the prostate cancer (Barry, 2001). In the United States (US), most prostate cancers are diagnosed through measurement of serum PSA. The serum PSA level correlates directly with prostate cancer risk and aggressiveness, as well as the outcomes after treatment. PSA testing is also useful in monitoring patients for tumor recurrence after treatment (Loeb & Catalona, 2007). The *HER2/neu* gene or protein has been found over-expression in 10% to 34% of breast cancers. It has been used as a diagnostic biomarker and also a treatment target in breast cancer. The clinical trial presented that systemic administration of anti-HER2 antibodies trastuzumab (Herceptin), alone and in combination with chemotherapy in patients with HER-2/*neu* overexpressing primary tumors, can increase the time to recurrence and overall response rates in metastatic breast cancer (Ross & Fletcher, 1998).

Gliomas are difficult to remove due to several reasons. Firstly, some drugs can not get into gliomas directly because of the blood-brain barrier. Secondly, the gliomas can infiltrate the tissues around them, the traditional approaches, including surgery, radiation therapy and chemo-therapy, can not get rid of them completely. Finally, gliomas may have more than one kind of tumor cells in them, so chemotherapy drug, which is only directed at one kind of tumor cells, can not kill the all tumor cells. Therefore, the investigations of glioma biomarkers for diagnosis, prognosis and therapy are an urgent mission for the scientist in future.

2. The research progress of glioma biomarkers

As far as we known, glioma biomarkers can be identified from the serum, cerebrospinal fluid, glioma cell lines or directly from glioma tissues. These biomarkers will help us to diagnose the gliomas in the earlier period, treat the glioma against the specific target and monitor the prognosis after treatment.

2.1 Diagnostic biomarkers for glioma

Currently, the examinations used in clinical diagnosis for glioma include computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, angiogram, skull x-ray, spinal tap, myelogram and biopsy. But it is still difficult to diagnose in the earlier period of gliomas, until if we can find some specific biomarkers associated with the early development of gliomas, the diagnosis will be easy to decide. Diagnostic (or screening) biomarkers are used to detect and identify a given type of cancer in an individual. These markers are expected to have high specificity and sensitivity (Kulasingam & Diamandis, 2008).

(1) YKL-40

YKL-40, also known as CHI3L1 or human cartilage glycoprotein-39, is a secreted glycoprotein. High levels of YKL-40 in serum have been implicated as a serum marker in a number of cancers including breast (Johansen et al, 1995; Jensen et al, 2003), colorectal (Cintin et al, 1999), and ovarian cancer (Dehn et al, 2003; Hogdall et al, 2003). Although the function of YKL-40 is not well elucidated, it is often over-expressed in epithelial cancers and gliomas. Previous studies suggested that YKL-40 was a marker associated with a poorer clinical outcome and a genetically defined histological subgroup of high-grade gliomas (Nutt et al, 2005). The YKL-40 was also implicated as an important marker of radiation therapeutic response and overall survival in glioblastoma (Pelloski et al, 2005).

Later, Hormigo et al. found that except for YKL-40, matrix metalloproteinase-9 (MMP-9) protein was also highly differentially expressed in malignant gliomas (Hormigo et al, 2006). YKL-40 and MMP-9 were determined by ELISA using serum samples from patients with gliomas, and the results indicated that the values correlated with the patient's radiographic status and survival. So, YKL-40 and MMP-9 may be used as a biomarker in glioma patients' serum and help confirm the absence of active disease in glioblastoma multiforme.

(2) GFAP

Another protein, glial fibrillary acidic protein (GFAP), first reported by Eng et al. in 1971, is a member of the cytoskeletal protein family and is widely detected in astroglial cells and neural stem cells (Eng et al, 1971, 2000; Doetsch, 2003; Jung et al, 2007). It is also expressed in astrocytoma and glioblastoma multiforme (Jacque et al, 1978; Hamaya et al, 1985; Abaza et al, 1998). A serum marker for malignant gliomas may improve both differential diagnoses with different histological subtypes and clinical management of glioma tumor patients. Jung et al. investigated GFAP levels in the serum of glioblastoma multiforme patients and various control groups. Their studies showed that the serum GFAP levels of these patients were significantly higher than those of patients with WHO grade II or III astrocytomas or of patients with brain metastases. And the serum GFAP concentration was closely linked with the glioblastoma volume and tumor necrosis volume imaged from magnetic resonance imaging scans. Therefore, the serum GFAP may be used as a diagnostic biomarker for glioblastoma multiforme. But it is necessary to evaluate whether the serum GFAP could be used to monitor therapeutic effects or have a prognostic value in future studies (Jung et al, 2007). Furthermore, it is reported that GFAP does not provide a better staining for distinguishing histologic subtypes of high-grade glioma by immunohistochemistry. Compared with GFAP, YKL-40 staining, is a stronger marker, provided a better class distinction. In addition, using a combination of YKL-40 and GFAP staining could afford even greater diagnostic accuracy (Nutt et al, 2005).

(3) Other potential biomarkers

Cerebrospinal fluid (CSF) was usually used to screen glioma biomarkers because of its closer relation with glioma and its relative ease of collection (Maurer et al, 2003). Furthermore, CSF has about 1000 proteins, which is 100~400 fold lower than in serum, and this will be facilitated to screen the specific protein biomarkers (Omenn, 2005). In the past decades, many markers have been found in CSF of glioma patients, such as S100, neuron-specific enolase (NSE), recoverin (protein A) and vascular endothelial growth factor (VEGF) (Gronowitz et al, 1984; Cochran & Wen, 1985; Taomoto et al., 1987; Sampath et al., 2004; Khwaja et al, 2007). However, these biomarkers could not be widespread used due to the limitation of repetition in CSF examinations.

Recently, new candidate biomarkers have been identified by proteomics analysis for CSF samples. For example, Khwaja et al. used two-dimensional gel electrophoresis (2-DE) and cleavable Isotope-Coded Affinity Tag (cICAT) to analyze CSF proteome to detect specific biomarkers in brain tumors with differing histologies and grades (Khwaja et al, 2007). Finally, 20 potential tumor-specific markers were specially identified in high-grade astrocytoma. These potential markers may also play important role in the development and malignant progression of human astrocytoma and will be the treatment targets in glioma.

Furthermore, exosome is now becoming a hot spot to look for cancer biomarkers. Exosomes are 50-90 nm vesicles-like objects secreted by various mammalian cells. An exosome is

formed intracellularly when a segment of cell membrane spontaneously invaginates and is endocytosed (Keller et al, 2006). It is reported that dendritic cells and B cells could secrete exosomes, which indicated that exosomes may play a functional role in mediating adaptive immune responses to pathogens and tumors (Li et al, 2006). Exosomes can also be detected in urine and they might serve as a diagnosis and treatment response marker in prostate cancer (Pisitkun et al, 2004; Nilsson et al, 2009). Therefore, exosomes, which are released from tumors into the blood, can also be used for diagnosis. The released exosomes by glioblastoma tumor cells contain mRNA, microRNA and angiogenic proteins (Balaj et al, 2011). Furthermore, the glioblastoma-derived exosomes serve as a vehicle to deliver genetic information and proteins in the tumor environment. Tumor mutations in glioma can be detected in exosomes from serum, which is also facilitating a blood-based biomarker detection for solid tumors (Skog et al, 2008). Thus, tumor-derived exosomes may be used as a diagnostic biomarker and aid in therapeutic decisions for glioma patients.

Although the histopathologic methods are often used to classify the pathologic grade of gliomas in clinical diagnosis, the results are usually subjective and less accurate. To overcome the limitations, cDNA microarray has been performed to screen diagnostic and prognostic markers for glioblastoma. The growth arrest and DNA-damage-inducible α (GADD45 α) and follistatin-like 1 (FSTL1) were over-expressed in most primary and secondary glioblastomas, whereas superoxide dismutase 2 and adipocyte enhancer binding protein 1 were up-regulated in the majority of primary glioblastomas (Reddy et al, 2008). All the results were validated by real-time reverse transcription quantitative PCR and immunohistochemical analysis. These findings suggested that GADD45 α and FSTL1 are glioblastoma-specific whereas superoxide dismutase 2 and adipocyte enhancer binding protein1 are primary glioblastoma-specific diagnostic markers. It is interesting to found that the diffusion parameters could also be evaluated as early biomarkers of disease progression in glioblastoma multiforme (Khayal et al, 2010).

2.2 Prognostic biomarkers for glioma

Tumor prognostic biomarkers are used once the tumor status has been confirmed. These biomarkers are expected to predict the probable course of the tumors including its recurrence, and they therefore have important influences on the aggressiveness of therapy (Kulasingam & Diamandis, 2008).

It is known that O(6)-methylguanine-DNA methyltransferase (MGMT) can recover the carcinogenic lesion in DNA induced by alkylating mutagens. What's more, it has been showed that methylation of the MGMT's promoter plays a significant role in carcinogenesis (Hegi et al, 2005). The hypermethylation in MGMT promoter has been detected in other various of human cancers, such as colon cancer, nonsmall-cell lung cancer, head and neck carcinoma, lymphomas, Leukemias, pancreatic carcinoma, melanoma, renal carcinoma and bladder carcinoma (Esteller et al, 1999). The hypermethylation frequency of MGMT promoter varies widely in different subtype glioma. It has ranged from 35% to 73% in glioblastoma, about 50%~84% in diffusely infiltrating anaplastic gliomas (World Health Organization grade III), as well as about 43%~93% in the WHO grade II counterparts (Deimling et al, 2011). Although the methylation of MGMT status appears to be a useful prognostic marker in the elderly patients with newly diagnosed glioblastoma (Gerstner et al, 2009). In fact, MGMT immunohistochemistry analysis had some lacks for routine diagnostic purposes due to the observer variability as well as lack of association with the MGMT promoter methylation status (Preusser et al, 2008).

As is known to all, the ras GTPase-activating-like protein IQGAP1 functions as a scaffold protein which is involved in cellular motility and morphogenesis (Mateer et al, 2003). It is participated in many signaling pathways to regulate cell adhesion, polarization and migration. For example, IQGAP1 was played as a VEGFR2-associated scaffold protein to organize ROS-dependent VEGF signaling, which could promote the migration and proliferation of endothelial cell to repair the injured vessels (Yamaoka-Tojo et al, 2004). It is also identified as a core component of neuronal motility signal transduction and it is involved in epithelial carcinogenesis and metastasis (Briggs & Sacks, 2003; Kholmanskikh et al, 2006; Balenci et al, 2006). But, one recent study found that IQGAP1 may be used as a marker to discriminate the human glioblastoma from oligodendroglioma (Balenci et al, 2006)

Another known protein, the insulin-like growth factor-binding protein 2 (IGFBP2) is usually detected in many human tumors, including malignancies of the lung, colon, adrenal glands, ovary, prostate, CNS and lymphoid tumors (Dunlap et al, 2007). Its overexpression is often linked with an increasingly malignant status of the tumor, indicating a potential oncogene function of IGFBP-2 in tumorigenesis (Hoeflich et al, 2001). IGFBP2 was also identified as a specific marker for central nervous system (CNS) tumors and might serve as a marker of tumor differentiation (Muller et al, 1994; Akmal et al, 1995). Furthermore, the plasma IGFBP2 levels are obviously higher in high-grade glioma patients than in low-grade glioma patients and healthy subjects. All these data indicate the plasma IGFBP2 has a biomarker's role in glioma (Lin et al, 2009).

The coexpression of IQGAP1 and IGFBP2 is strongly associated with poor prognosis in astrocytoma and oligodendroglioma. These findings might complement the WHO classification system to permit more precise classification for glioma subtypes. Besides, in glioblastoma patients who had shown long-term survival of >3 years after initial diagnosis, the expression of IQGAP1 and IGFBP2 were not be detected. Thus, the absence of IQGAP1 and IGFBP2 may be a good prognostic marker in glioblastoma patients. However, the relationship between IQGAP1 and IGFBP2 and their roles in glioma biology are still need to be elucidated in future (McDonald et al, 2007).

Matrix-assisted laser desorption ionization- mass spectrometry (MALDI-MS) is a high-throughput and accurate tool in proteomics research. It has been used to profile the glioma-specific protein patterns which can provide clinically relevant information on tumor malignancy. The glioma-specific protein patterns could accurately classify glioma subtypes and discriminate patient survival patterns. Still, there are several discriminatory proteins were identified, including calyculin, dynein light chain 2 (DLD2), calpactin I light chain, astrocytic phosphoprotein (PEA-15), fatty acid-binding protein 5 (FABP5) and tubulin - specific chaperone A. These proteins were reported to be involved in various aspects of tumorigenesis. These differential expression proteins in gliomas may provide as diagnostic and prognostic markers (Schwartz et al, 2005).

Tumor is a disease coupled with multiple gene alterations. The gene expression pattern may predict the survival time in patients with high-grade gliomas independently of other factors (Czernicki et al, 2007). Proteins are the true executors that directly perform functions regulated by genes. Therefore, the protein changes would be more attractive in cancer biomarker discovery (Liang et al, 2011). Khalil used the two-dimensional difference gel electrophoresis (2D-DIGE) compared protein patterns between glioma tissues and non-tumor brain tissues. About 20 unique differential proteins were identified, and these proteins with diagnostic or prognostic value are still needed to be validated in future

research (Khalil, 2007). In addition, the gelsolin protein is significantly lower expressed in the increasing glioma histopathologic grade. And in astrocytoma, the overall survival in the low-expression group was significantly poorer than in the high expression group. Therefore, gelsolin may be a prognostic marker for astrocytoma patients (Ohnishi et al, 2009). Besides, the B-chain of α_2 -heremans-schmid glycoprotein in serum can be used as a potential biomarker for glioma prognosis (Petrik et al, 2008).

DNA microarray is usually used to measure gene expression levels, single nucleotide polymorphisms or genotype. It is one of the fastest-growing new technologies in cancer research. By DNA microarray, it was found that metalloproteinase-4 (TIMP-4) and its putative partner CD63 were coexpressed in glioblastomas and pilocytic astrocytomas. High TIMP-4 /CD63 co-expression level has been found to be an independent prognostic marker associated with progression and shorter survival in glioblastomas. On the contrary, the higher co-expression indicated adverse outcomes in diffuse astrocytoma and oligoastrocytoma patients (Rorive et al, 2010). Similarly, a high level of osteopontin protein in serum indicates a poor prognosis in glioblastoma patients, and it may be a poor prognostic biomarker in glioblastoma patients (Sreekanthreddy et al, 2010).

Gene mutation is another factor in carcinogenesis. Recently, the isocitrate dehydrogenase 1 (IDH1) was analyzed by direct sequencing in a series of 404 glioma patients with different grade. It is found that the mutation rates in the codon 132 of IDH1 were obviously decreased with increasing glioma grade, which indicated that the codon 132 mutations of IDH1 could be an important prognostic marker in grade 2 to 4 gliomas (Sanson et al, 2009). The codon 132 mutation of IDH1 was detected in more than 70% of WHO grade II - III astrocytomas, oligodendrogliomas, as well as in glioblastomas which are developed from those lower-grade gliomas. Gliomas, without mutations in IDH1 codon 132, often had mutations in codon 172 of the IDH2 gene. The results showed that patients with such mutations in IDH usually had a better prognosis than those with wild-type IDH genes (Yan et al, 2009).

2.3 Therapeutic targets for glioma

Recent developments in the field of tumor biology have elucidated signalling pathways and genes involved in the development of gliomas, which represent new potential therapeutic targets, and many targeted therapies are currently being tested in clinical trials (Sanson, 2008).

(1) Receptor tyrosine kinases (RTKs)-mediated signaling

The antiangiogenesis strategy has been widely used in molecularly targeted therapy for malignant glioma. Angiogenesis in tumors is caused by a number of factors involved in many signaling pathways, in which the VEGF-VEGFR2 is a major and more attractive pathway. Currently, many angiogenesis inhibitors or antibodies have been applied in clinical studies. These inhibitors or antibodies were usually design to anti-specific factors, including VEGF itself, VEGFR, and other upstream /downstream factors regulated the VEGF signaling pathway, such as Cox-2, HIF-1 α , and so on (Chi et al, 2009).

Gliomas are highly heterogeneous in terms of biological alterations. Mutations in *EGFR* and genes for other receptor tyrosine kinases (RTKs), namely platelet-derived growth factor (*PDGFR*), *HER2/neu* and *MET*, lead to activation of downstream PI3K-AKT and ERK-MEK pathways in gliomas. Therefore, several antiangiogenic inhibitors, which downregulate EGFR-mediated signaling, have recently been developed and tested as therapeutic agents, including cediranib (Recentin, AstraZeneca), vatalanib (Novartis Pharmaceuticals, Basel,

Switzerland), sunitinib (Sutent, Pfizer), sorafenib (Nexavar, Bayer Pharmaceuticals, Leverkusen, Germany), vandetanib (Zactima, AstraZeneca) and VEGF trap (Aflibercept, Regeneron Pharmaceuticals, NY, USA) (Lukas et al, 2009; Roesler et al, 2010). Besides small-molecule inhibitors, therapies can be targeted to tumor cells (e.g., EGFR inhibitors) or tumor blood vessels with the monoclonal antibody against VEGF, bevacizumab (Avastin; Genentech, CA, USA).

However, followed by the antiangiogenesis therapy at long time, the patients will have a high resistance to anti-VEGF therapies. Soda et al. investigated the resistance mechanism of anti-VEGF therapy to glioma in the transduction of p53+/- heterozygous mice containing oncogenes and in the GFAP-Cre recombinase (Cre) mice. It was found that mouse glioblastoma cells could be transdifferentiated into vascular endothelial cells (tumor-derived endothelial cells, TDECs) in the hypoxia situation, and this process was independent of VEGF. A further study has showed that the formation of TDECs are also presented in the xenograft model of human glioblastoma spheres directly from the patients with glioblastoma (Sodaa et al, 2011). These studies show that the TDECs may have an important role in the resistance to anti-VEGF therapy, and hence they could be a candidate target for glioblastoma therapy. But there are still many questions need to be answered. For example, what are the signaling molecules that participate in the production of TDECs? Is this mechanism of VEGF-A resistance uniform to all glioblastoma or are there alternate pathways used for different subsets of glioblastoma? (Sodaa et al, 2011; Hormigo et al, 2011).

(2) PI3K/AKT/mTOR pathways

PI3K pathways regulate several malignant phenotypes including antiapoptosis, cell growth, and proliferation. Activation of PI3K pathway is associated with poor prognosis in glioma patients (Sathornsumetee et al, 2007). Activated PI3K phosphorylates several downstream effectors including AKT. AKT is a serine/threonine kinase that regulates cell growth, proliferation, and apoptosis. The mTOR is a serine/threonine kinase downstream from AKT. Several mTOR inhibitors have been studied in the treatment of malignant glioma. These include sirolimus (Rapamune; Wyeth Pharmaceuticals, Madison, NJ) FDA-approved for the prophylaxis of solid organ transplant rejection, and temsirolimus (CCI-779, Torisel; Wyeth Pharmaceuticals) FDA-approved for use in renal cancer (Lukas et al, 2009). And everolimus (RAD001; Novartis Oncology, East Hanover, NJ) and deferolimus (AP23573; ARIAD/Merck), still experimental, have all been evaluated in clinical trials alone or in combination with other therapies in gliomas. Although data strongly support the view of the PI3K-AKT-mTOR pathway as an important target, current clinical results on the use of mTOR inhibitors remain disappointing. For example, the Phase II studies using temsirolimus as monotherapy found only limited activity in recurrent glioblastoma multiforme. Because pathways are complex interactive networks characterized by cross-talk and homeostatic feedback loops that can greatly influence response to therapy.

(3) Histone deacetylase (HDAC)

Histone deacetylases (HDACs), regulating histone acetylation, are now considered to be a promising target for gliomas. The epigenetic therapies, particularly HDAC inhibitors (HDACis), have been proposed as potential novel drugs. Suberoylanilide hydroxamic acid (SAHA, vorinostat, Zolinza; Merck), FDA-approved for cutaneous T-cell lymphoma, is being evaluated in clinical trials of multiple cancers, including malignant gliomas (Sathornsumetee et al, 2007; Roesler et al, 2010).

(4) Other targets and therapeutic approaches

Advances in the understanding of cellular and molecular alterations in gliomas have led to the emergence of experimental molecularly targeted therapies. The targeted therapies for glioma include small molecules and antibodies targeted at growth factor pathways, intracellular signaling cascades and epigenetic molecular targets, as well as RNAi, gene therapy and neural stem cells as therapeutic tools (Roesler et al, 2010).

The receptor protein tyrosine phosphatase β (RPTP β) have a role to facilitate tumor cell adhesion and migration by interactions with extracellular matrix components and the growth factor pleiotrophin. Over-expression of RPTP β was found in several types of solid tumor, but with low expression in normal tissue (Foehr et al, 2006). It is reported that RPTP β was displayed strong staining in oligodendrogliomas, and may be a novel oligodendroglioma marker (Hägerstrand et al, 2008). Therefore, RPTP β may perform a role of potential therapy target in gliomas and other tumors. The monoclonal antibodies of RPTP β obtained from immunizing mice could kill glioma cells in vitro and significantly suppress the growth of human glioma tumors in a xenograft mouse model (Foehr et al, 2006).

The PBEF1 (Pre-B-cell colony enhancing factor 1) gene may be a potential malignant astrocytoma serum marker and prognostic indicator in glioblastoma (Reddy et al, 2008). PBEF1 gene encodes nicotinamide phosphoribosyltransferase (NMPRTase), which has an important role in the salvage pathway of NAD⁺ biosynthesis. The inhibitor of NMPRTase, such as FK866, can reduce cellular NAD⁺ levels and induce apoptosis in tumors (Khan et al, 2006). Therefore, the novel inhibitor of NMPRTase may be used as an anti-tumor drug in glioma therapy (Chandra et al, 2011).

However, targeting a single component of cell signaling, or a single signaling pathway, is not likely to effectively reduce tumor growth in glioma patients. Preclinical studies should characterize the effects of multi-targeted inhibitors, combining several targeted inhibitors, and combining targeted therapies with cytotoxic chemotherapy.

Tumor stem cells are a kind of specific tumor cells which have the stem cell like properties. It is reported that glioma stem cells display self-renewal and proliferation properties, unlimited life span, a high migration rate and resistance to chemotherapy, and they are capable of replenishing the whole tumor cell population (Singh et al, 2003; 2004). The glioma stem cells have been involved in many signaling pathways, including Notch, Hedgehog, Wnt, Myc, PI3K and MAPK cascades, and so on (Das et al, 2008; Li et al, 2009; Roesler et al, 2010). According to the important roles of glioma stem cells, the drugs that directly and specifically kill the glioma stem cells will be more effective than other ways in glioma therapy. Some studies have proposed the possible strategies to target the glioma stem cells. One way is using differentiating agents (like bone morphogenetic proteins, BMPs) to induce the glioma stem cells into mature, astrocytic cells, and another way is regulating the expression of targeting genes involved in glioma stem cell proliferation (Piccirillo et al, 2006; Horvath et al, 2006).

3. Discussion and outlook

It is clear that more and more high-throughput, accurate technologies or strategies have been used in identification of glioma biomarkers (shown in Figure 1). These techniques include ELISA (Hormigo et al, 2006; Lin et al, 2009; Sreekanthreddy et al, 2010), 2-DE (Khwaja et al, 2007; Khalil, 2007; Ohnishi et al, 2009), DNA microarray (Reddy et al, 2008),

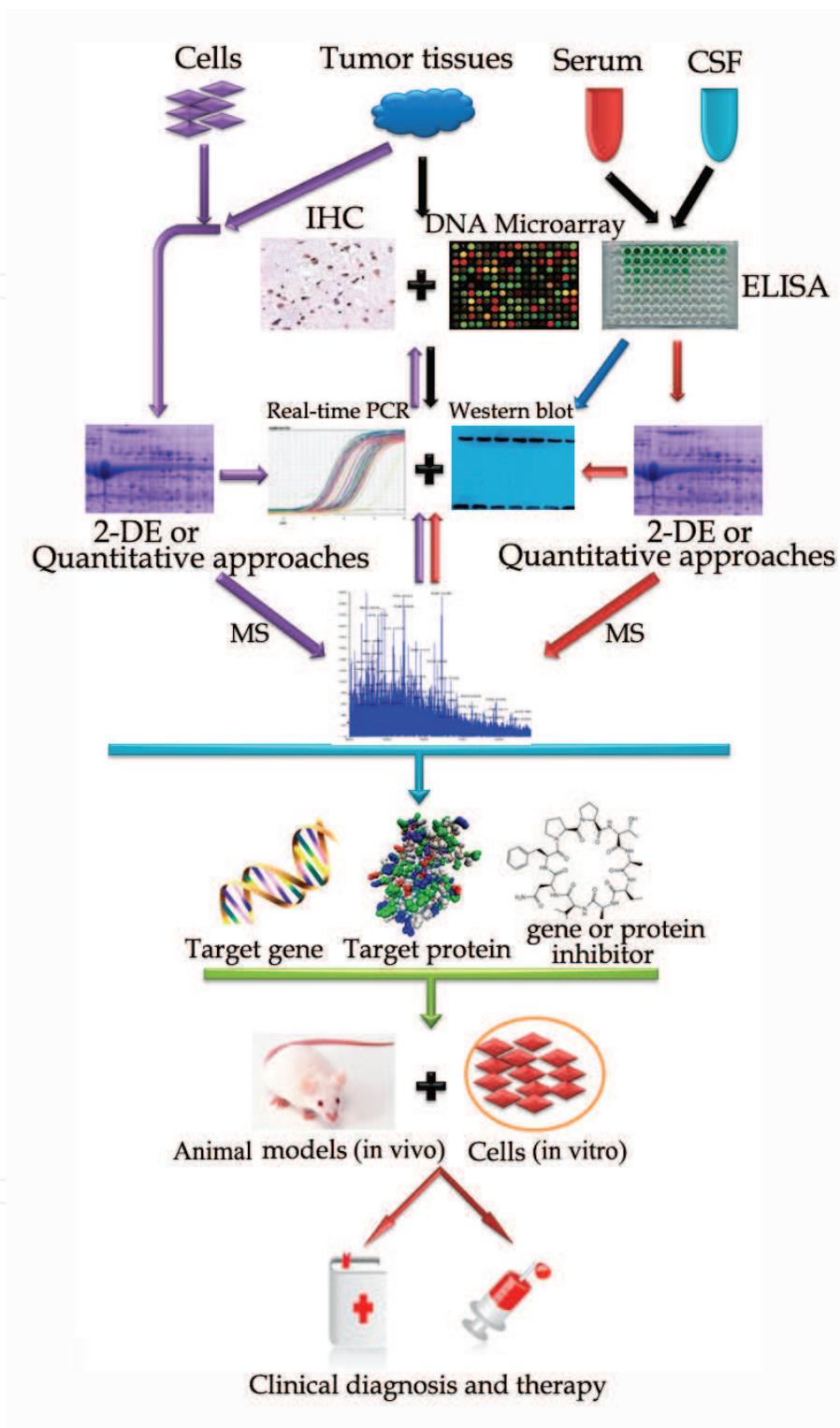


Fig. 1. Current different techniques are used in the glioma biomarker discovery.
 a. CSF: Cerebrospinal fluid; IHC: immunohistochemistry; ELISA: enzyme linked immunosorbent assay; 2-DE: two-dimensional electrophoresis; MS: mass spectrometry.
 b. The quantitative approaches here contain the isotope-coded affinity tag (ICAT), stable isotope labeling with amino acids in cell culture (SILAC), isobaric tagging for relative and absolute quantitation (iTRAQ).

MALDI-MS or SELDI-TOF -MS (Petrik et al, 2008; Schwartz et al, 2005), direct sequencing (Sanson et al, 2009), ICAT (Khwaja et al, 2007), and transgenic mouse etc (Sodaa et al, 2011). A number of quantitative approaches summarized in Figure 1, with different technical advantages and challenges, have been developed for glioma biomarker discovery. However, many complementary technologies are being developed and either alone or in combination will undoubtedly allow their potential in biomedical research and translation into clinical practice.

Recently, we have investigated the protein profiling in low-grade gliomas by a quantitative SILAC (stable isotope labeling with amino acids in cell culture) -based proteomics strategy in order to screen novel glioma-specific proteins (Liang et al, 2009a; Shen et al, 2010). Besides, the quantitative proteomics strategy also contains the isotope-coded affinity tag (ICAT), isobaric tagging for relative and absolute quantitation (iTRAQ), and so on. With these high-throughput and sensitive approaches, more specific glioma biomarkers will be identified (Liang et al, 2009b).

In conclusion, the glioma biomarkers primarily can be classed into three kinds, including diagnostic biomarkers, prognostic markers and therapeutic targets. In fact, only few biomarkers could be used in clinical applications, such as O⁶-methylguanine-DNA methyltransferase (MGMT) (Gerstner et al, 2009; Deimling et al, 2011), VEGF and VEGFR (Chi et al, 2009), and so on (shown in Table 1). The other potential biomarkers for glioma are

Target gene/protein	Clinical Application	Phase	Drug
MGMT (Methylguanine methyl transferase)	diagnosis and prognosis	---	---
EGFR (Epidermal growth factor receptor)	therapy	Phase II	MAB-425
		---	Erlotinib
		Phase III	Nimotuzimab
		Phase I/II	Gefitinib
		Phase I/II	Cetuximab
VEGF (Vascular endothelial growth factor)	therapy	Phase II	Bevacizumab / Irinotecan
VEGFR (Vascular endothelial growth factor receptor)	therapy	Phase I/II	Vatalanib
PDGFR (Platelet-derived growth factor receptor)	therapy	Phase II	Crenolanib (CP-868,596)
		Phase II	Nilotinib
		Phase I/II	Imatinib
mTOR (mammalian target of rapamycin)	therapy	Phase III	Everolimus
		Phase II	Temsirolimus
		Phase I	Sirolimus+Gefitinib
HDAC (histone deacetylase)	therapy	Phase I/II	SAHA
COX-2 (cyclooxygenase-2)	therapy	Phase I/II	Celecoxib

Table 1. Glioma biomarkers in clinical applications

Target gene/ protein (or other object)	Candidate Applications	Localization (a)	References
YKL-40	Diagnosis & prognosis	Serum or tumor tissues	Nutt et al, 2005; Hormigo et al, 2006
MMP-9	Diagnosis & prognosis	Serum	Hormigo et al, 2006
GFAP	Diagnosis & prognosis	Serum or tumor tissues	Nutt et al, 2005; Jung et al, 2007
Exosomes	Diagnosis	Serum or tumor tissues	Skog et al, 2008; Balaj et al, 2011
GADD45 α and FSTL1	Diagnosis	Tumor tissues	Reddy et al, 2008
Diffusion parameters	Diagnosis	Tumor tissues	Khayal et al, 2010
MGMT	Diagnosis & prognosis	Tumor tissues	Gerstner et al, 2009
IQGAP1	Diagnosis & prognosis	Tumor tissues	Balenci et al, 2006; McDonald et al, 2007
IGFBP2	Diagnosis & prognosis	Serum or tumor tissues	McDonald et al, 2007; Lin et al, 2009
*Calcyclin,*DLC2 , *CalpactinI light chain, *PEA-15, *FABP5, *Tubulin-specific chaperone A	Diagnosis & prognosis	Tumor tissues	# Schwartz et al, 2005 (b)
AHSG	Prognosis	Serum	Petrik et al, 2008
Gelsolin	Prognosis	Tumor tissues	Ohnishi et al, 2009
IDH1/IDH2 mutation	Prognosis	Tumor tissues	Sanson et al, 2009, Yan et al, 2009
TIMP-4/CD63	Prognosis	Tumor tissues	Rorive et al, 2010
Osteopontin protein	Prognosis	Serum	Sreekanthreddy et al, 2010
FoxM1	Therapy	Tumor tissues	Liu et al, 2006
RPTP β	Diagnosis & therapy	Tumor tissues	Foehr et al, 2006, Hagerstrand et al, 2008
PBEF1(NMPRTase)	Prognosis & therapy	Serum or tumor tissues	Reddy et al, 2008, Chandra et al, 201
Glioma stem cells	Therapy	Tumor tissues	Piccirillo et al, 2006; Horvath et al, 2006
TDECs (tumor -derived endothelial cells)	Therapy	Tumor tissues	Sodaa et al, 2011; Hormigo et al, 2011

a. The sample pool where the biomarkers were identified.

b. The biomarkers with * tag were identified in the same study with # tag.

Table 2. Some novel potential glioma biomarkers

promised to need a further validation and confirmation (shown in Table 2). There have some limitations for application of glioma biomarkers in the clinical trial. Firstly, the specification of biomarkers is always not certainly. Because of the biomarkers are usually detected in both normal and tumor samples, and other diseases can also cause the changes of biomarkers. And then, the investigation strategy of biomarkers are significantly various. Even if used the same type samples, the results will be remarkably difference. Finally, the patients with tumors are usually difference from each other, also called the individual difference. Besides, the overall samples used in biomarker identification are still limited due to various gaps. In spite of this, the studies of glioma biomarker identification still have a bright future by the continuous efforts of biologists.

4. Acknowledgments

This work was financially supported by the grants from National Key Basic Program of China (2011CB910703), National Natural Sciences Foundation of China (30970654, 31071235), Program for New Century Excellent Talents in University (NCET-10-0595) and Sichuan Science Research Program for Young Scholars (2010JQ0016).

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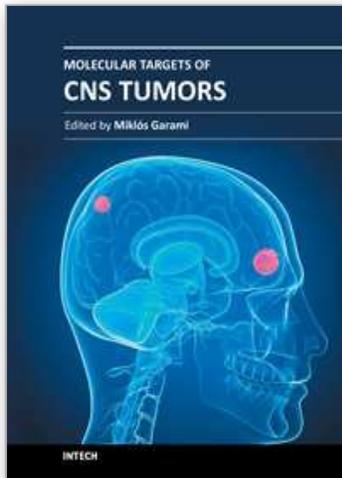
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Molecular Targets of CNS Tumors

Edited by Dr. Miklos Garami

ISBN 978-953-307-736-9

Hard cover, 674 pages

Publisher InTech

Published online 22, September, 2011

Published in print edition September, 2011

Molecular Targets of CNS Tumors is a selected review of Central Nervous System (CNS) tumors with particular emphasis on signaling pathway of the most common CNS tumor types. To develop drugs which specifically attack the cancer cells requires an understanding of the distinct characteristics of those cells. Additional detailed information is provided on selected signal pathways in CNS tumors.

How to reference

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

Shufang Liang and Guobo Shen (2011). Biomarkers of Glioma, Molecular Targets of CNS Tumors, Dr. Miklos Garami (Ed.), ISBN: 978-953-307-736-9, InTech, Available from: <http://www.intechopen.com/books/molecular-targets-of-cns-tumors/biomarkers-of-glioma>

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