CURRENT PERSPECTIVE OF THERAPIES TO GLIOMAS EXPRESSING
HEPATOCYTE GROWTH FACTOR

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ABSTRACT

This paper presents about glioblastoma multiforme (GBM) as the most common malignant brain tumor of the central nervous system (CNS), with the purpose to investigate the scatter factor/hepatocyte growth factor (SF/HGF) and other current perspective therapies involved in the therapeutic interventions of CNS tumors which would provide excellent tumor control and regression, and may improve the prognosis and quality of life of patients with neurological tumors.

Keyword: Gliomas, hepatocyte growth factor, therapeutic intervention, prognosis

INTRODUCTION

Glioblastoma multiforme is the most common malignant brain tumor with a 2-year survival rate of 26.5% for patients treated with surgery, radiation and temozolomide. The median age at diagnosis is 64 years; (1) however, it is the second most common cause of cancer-related deaths in young adults (2). Despite advances in surgery, chemotherapy, radiotherapy and the development of novel treatments such as the slow-release polymer, Gliadel and the vascular endothelial growth factor (VEGF) inhibitor, Avastin, the prognosis for patients with malignant gliomas has improved only slightly over the past few decades with a median survival of less than 15 months. The malignant phenotype associated with glioblastoma includes rapid and uncontrolled growth of glial cells, impaired cell death, distant invasion and migration of glioma cells into the surrounding brain. The combination of chemotherapy and radiation has demonstrated an important role in the treatment of glioblastoma, with substantial benefits when compared with either treatment alone (3). The side effects of radiation, such as the radio-necrosis that may occur beyond certain doses, or systemic effects of chemotherapeutic agents such as procarbazine, lomustine and vincristine limit the overall effectiveness of these therapies in the treatment of glioblastoma, when used in isolation (4,5).

The malignant progression of glioblastoma has been shown to be influenced by the altered expression of growth factors/cytokines and their receptors. These growth factors include, but are not limited to, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and recently recognized hepatocyte growth factor (HGF) also known as scatter factor (SF) and its only known receptor c-Met (6-10). As such, targeting these receptor tyrosine kinase systems is expected to yield substantial improvement in the patient's prognoses. Furthermore, recent advances in targeted molecular therapies have uncovered complex interactions between cell surface receptors and intracellular signaling second messenger systems. Signal transduction pathways can influence tumor phenotypes, which include tumor cell proliferation, apoptotic cell death, tumor angiogenesis and cellular interactions with the surrounding extracellular matrix (11-13). The fundamental characteristics of the tumor cell is to survive and grow beyond normal homeostatic environment. Recent research interests have focused on the development of inhibitors targeting these signaling pathways to inhibit growth of tumor cells and also reducing side effects. Several small molecule inhibitors have been developed and demonstrated profound effects in other cancer subtypes such as myeloid leukaemia (14) and lung cancer (15). This review discusses the use of receptor tyrosine kinase (RTK) targeted therapies in patients diagnosed with glioblastomas that express (HGF) and its receptor c-Met (HGF:c-Met).
HEAPATOCYTE GROWTH FACTOR AND ITS ONLY KNOWN RECEPTOR C-MET

Scatter factor (SF) was originally characterized in 1987 as a fibroblast-derived epithelial cell motility factor and also as hepatocyte growth factor, a potent mitogen of primary cultured hepatocytes in 1989. The gene encoding HGF is located on chromosome 7q21.1 (19). HGF is a multifunctional and multi-domain, heterodimeric, plasminogen-related-heparin-binding glycoprotein. HGF contains a 69KDa α-chain with four kringle domains, and a 34kDa β chain, containing a serine protease-like domain with no enzymatic activity (16,20,21). The only known receptor for HGF is c-Met, a transmembranous RTK that is also a proto-oncogene. C-Met is a 190KDa, disulfide-linked heterodimer, which is formed by cleavage of a precursor protein at furin site located between residue 307 and 308. C-Met contains a 50KDa extracellular α-subunit linked by a disulfide bridge to a 140KDa tyrosine like β-subunit. The beta-chain traverses the membrane and contains the cytoplasmic kinase domain and a carboxy terminal that are essential for its downstream signal transduction (20,22,23). The alpha subunit of the c-Met receptor is extra-cellular along with the first 212 residues of the beta subunit that binds with HGF.

HGF:C-MET: BIOLOGICAL FEATURES

HGF and c-Met are expressed in a wide range of normal human tissues and each plays an important role in morphogenesis, organogenesis, wound healing, and tissue regeneration (24,25). Analysis of HGF or c-Met knockout mice demonstrates identical phenotypes with aberrations in development with severely impaired placentas and livers and mice dying within uterus (20,26). HGF regulates various developmental processes via epithelial mesenchymal interactions. During development, c-Met is expressed on the epithelial cells of many organs, while HGF is produced by adjacent mesenchymal cells (27). HGF and c-Met expression levels are upregulated in injured organs such as the heart, liver and kidney. HGF and c-Met promote cell proliferation and migration and also inhibit cell death (20,28).

HGF:C-MET IN CANCER

Over activation and/or dysregulation of HGF/c-Met signaling correlate with poor prognosis in patients diagnosed with many human malignancies (20). Furthermore, the expression levels of these two proteins correlate with an increased malignant phenotype in numerous carcinomas and human solid tumors. Several lines of experimental evidence support HGF/C-Met’s role in malignancy. For instance, tumor cells engineered to overexpress HGF and/or c-Met show increased malignant potential in vitro and in animal models (29,30). Conversely, down-regulation of c-Met and/or HGF correlates with decreased tumorigenicity in animal models (31). The c-Met gene is amplified in some human tumors and germline-activating mutations have also been found in both inherited and sporadic forms of some cancers, such as renal papillary carcinoma (32-34). More recently, it has been shown that c-Met amplification serves as an escape mechanism for lung carcinomas that initially respond and then become resistant to epidermal growth factor receptor (EGFR) inhibitors (35).

HGF:C-MET IN GLIOBLASTOMAS

Almost all human glioblastoma specimens studied express c-Met and 50% of them express HGF. Lamszus et al(36) analyzed 74 human clinical low or high-grade glioma samples and showed that nearly all the high grade gliomas expressed HGF (36). HGF levels were reported to be significantly higher in high grade gliomas compared with lower grades and HGF/c-Met expression levels were often correlated with poor prognosis (36-38). At the cellular level, HGF can exert its effects in an autocrine and/or paracrine manner via c-Met activation protecting cells from death by cytotoxic agents, and also enhancing invasion, tumor cell proliferation, angiogenesis and inhibiting apoptosis (37,39). HGF gene transfer to glioma cells enhances malignant progression, tumor growth and tumor associated angiogenesis, while inhibition of HGF or c-Met inhibits glioma growth both in vitro and in vivo (30,31,40,41). HGF and c-Met gene knockdown in vivo via U1/Ribozymes (a chimeric transgene designed to inhibit HGF or c-Met expression) inhibits established glioma growth and prolongs survival in nude mice bearing intracranial HGF-expressing gliomas(31). Because of the compelling evidence in support of HGF/c-Met’s role in brain tumor malignancy, treatments aimed at this receptor/cognate ligand system have received considerable attention. Several small molecule inhibitors have been developed to target this signal transduction pathway. Christensen et al(42) developed a small molecule c-Met tyrosine kinase inhibitor (PHA-6655752), with anti-tumor activity in a systemic xenograft cancer model (42).

RTK THERAPEUTICS

Targeting growth factors or their receptors, through directed therapeutics is a treatment option that has produced exciting results, so far. Small molecule inhibitors such as gefitinib and erlotinib bind to the intracellular tyrosine kinase domain of the epidermal growth factor receptor competing with adenosine triphosphate (43). Gefitinib and erlotinib have shown promise in non-small cell lung adenocarcinoma, and preclinical studies have demonstrated evidence of
effectiveness in a wide variety of solid tumors. Both drugs have shown a modest benefit in glioma clinical trials initially, but further studies demonstrated conflicting data and disappointed clinical responses \(\text{\textsuperscript{(44).}}\) Several small molecule c-Met tyrosine kinase inhibitors have also been developed that inhibit c-Met-dependent phenotypes in vitro, in vivo and clinical trials with these molecules are on the horizon \(\text{\textsuperscript{(42,45-47).}}\)

Monoclonal antibodies, another approach to targeting RTKs and their ligands, have shown promise against a wide variety of neoplasms. There are about 20 mAbs approved for clinical use in the USA, with eight currently approved for cancer therapy. Some of the most successful mAbs are Trastuzumab (Herceptin\textsuperscript{\textregistered}), a mAb directed to the HER-2 receptor for treatment of breast cancer; Cetuximab (Erbitux\textsuperscript{\textregistered}), an anti-EGF receptor mAb for treatment of colon cancer; and Bevacizumab (Avastin\textsuperscript{\textregistered}), an antibody to (VEGF) also used to treat colon cancer, lung cancer, and glioblastoma.

**ANTI-HGF THERAPEUTICS**

Recently, Galaxy Biotech developed a neutralizing murine mAb (mL2G7) against human HGF and found potent in-vitro and in-vivo activity of mL2G7 against human HGF-expressing glioma xenografts \(\text{\textsuperscript{(48).}}\) The Laterra lab in collaboration with Dr. Kim found that systemic mL2G7 therapy showed robust inhibition of growth in an intracranial U87MG glioma (HGF+/c-Met+ human glioma). Anti-HGF therapeutics also inhibited blood vessel density, tumor cell proliferation and induced apoptosis. Galaxy Biotech has humanized L2G7 (huL2G7, TAK-701), which is under clinical trials. Several pharmaceutical companies have followed suit developing neutralizing fully humanized anti-HGF mAb that have similar anti-tumor activity against glioma xenografts models \(\text{\textsuperscript{(49).}}\) These clinical associations and experimental data have stimulated the development of agents to therapeutically target HGF:c-Met signaling.

Despite the strong association between HGF/c-Met expression levels and tumor grade/poor outcomes, it is likely that the growth of only a subset of c-Met/HGF tumors will depend on the c-Met pathway and respond to L2G7. Tumor-promoting mutations in parallel mitogenic pathways such as EGFR amplification, PDGFR\textsuperscript{\textregistered} amplification, and EGFR\textsuperscript{\textregistered} expression are commonly observed in malignant gliomas (50-52). Also, oncogenic mutations at points downstream of c-Met activation such as loss of the tumor suppressor PTEN, which leads to over-activation of Akt, can occur \(\text{\textsuperscript{(53,54).}}\) The relatively high frequency of these genotypes makes it imperative that we understand their influence on glioma sensitivity to anti-HGF therapeutics.

**CURRENT PERSPECTIVE**

If the HGF:c-Met pathway was the only driver of glioblastomas malignancy, then the above-mentioned therapeutic interventions would provide excellent tumor control and/or regression, in addition to increasing the quality of life of patients; unfortunately for a significant number of patients, this notion does not hold true. Only a subset of primary human tumors express elevated levels of HGF and anti-HGF therapy is presumed to only be effective when HGF levels are elevated. Several studies have demonstrated that primary human gliomas express a wide array of growth factors and receptor tyrosine kinase systems that can contribute to parallel activation of signal transduction pathways in malignant gliomas \(\text{\textsuperscript{(47,55).}}\) Several studies have investigated the oncogenic signaling pathways involved in malignant glioma formation and progression and examined the tumor growth and oncogenic signaling responses to anti-HGF therapeutics in an HGF/c-Met glioma model that express co-activated receptor tyrosine kinases, such as EGFR\textsuperscript{\textregistered}VIII, c-Kit, and PDGFR \(\text{\textsuperscript{(47,55,56).}}\) As the armamentarium of drugs and treatment strategies for malignant gliomas expands, it is imperative that we understand the underlying mechanisms by which these therapies act. Understanding the genetic determinants of response, as well as the underlying treatment mechanisms will allow us to harness the full potential of these agents in order to find a cure for this disease.

**CONFLICT OF INTEREST**

The authors declare that they have no competing interests.

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