CURRENT PERSPECTIVE OF THERAPIES TO GLIOMAS EXPRESSING HEPATOCYTE GROWTH FACTOR

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ABSTRACT

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

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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 it's 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 kringledomains, 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 disappointing clinical responses (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 (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®), a mAb directed to the HER-2 receptor for treatment of breast cancer; Cetuximab (Erbitux®), an anti-EGF receptor mAb for treatment of colon cancer; and Bevacizumab (Avastin®), 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 (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 (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, PDGFRA amplification, and EGFRvIII 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 (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 (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 EGFRvIII, c-Kit, and PDGFR (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.

REFERENCES

1. Schwartzbaum JA, Fisher JL, Aldape KD et al. Epidemiology and molecular pathology of glioma. Nature clinical practice Neurology 2006: 2: 494-503.

2. Primary Brain Tumors in the United States, Statistical Report, Years of Data Collected. In. Hinsdale: Central Brain Tumor Registry of the United States; 2000-2004:1-62 :2008.

3. Stupp R, Mason WP, van den Bent MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005:352: 987-996

4. Stewart LA.Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. Lancet 2002:359: 1011-1018

5. Stupp R, Hegi ME, Mason WP et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. The lancet oncology 2009:10: 459-466

6. Abounader R, Laterra J. Scatter factor/hepatocyte growth factor in brain tumor growth and angiogenesis. Neuro-oncology 2005:7: 436-451

7. Berkman RA, Merrill MJ, Reinhold WC et al. Expression of the vascular permeability factor/vascular endothelial growth factor gene in central nervous system neoplasms. J Clin Invest1993: 91: 153-159

8. Maxwell M, Naber SP, Wolfe HJ et al. Expression of angiogenic growth factor genes in primary human astrocytomas may contribute to their growth and progression. Cancer research 1991:51: 1345-1351

9. Nister M, Claesson-Welsh L, Eriksson A et al.Differential expression of platelet-derived growth factor receptors in human malignant glioma cell lines. J Biol Chem 1991:266: 16755-16763

10. Shweiki D, Itin A, Soffer D et al. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. Nature 1992:359: 843-845

11. Romashkova JA, Makarov SS. NF-kappaB is a target of AKT in anti-apoptotic PDGF signalling. Nature 1999:401: 86-90

12. Tsatas D, Kanagasundaram V, Kaye A et al. EGF receptor modifies cellular responses to hyaluronan in glioblastoma cell lines. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2002:9: 282-288

13. Tsatas D, Kaye AH. The role of the plasminogen activation cascade in glioma cell invasion: a review. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2003:10: 139-145

14. Goldman JM, Melo JV. Targeting the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001:344: 1084-1086

15. Baselga J, Albanell J. Targeting epidermal growth factor receptor in lung cancer. Curr Oncol Rep 2002: 4: 317-324

16. Nakamura T, Nishizawa T, Hagiya M et al. Molecular cloning and expression of human hepatocyte growth factor. Nature 1989:342: 440-443

17. Miyazawa K, Tsubouchi H, Naka D et al. Molecular cloning and sequence analysis of cDNA for human hepatocyte growth factor. Biochemical and biophysical research communications 1989:163: 967-973

18. Stoker M, Gherardi E, Perryman M et al. Scatter factor is a fibroblast-derived modulator of epithelial cell mobility. Nature 1987:327: 239-242

19. Saccone S, Narsimhan RP, Gaudino G et al. Regional mapping of the human hepatocyte growth factor (HGF)-scatter factor gene to chromosome 7q21.1. Genomics 1992: 13: 912-914

20. Birchmeier C, Birchmeier W, Gherardi E et al. Met, metastasis, motility and more. Nature reviews 2003: 4: 915-925

21. Lokker NA, Mark MR, Luis EA et al. Structure-function analysis of hepatocyte growth factor: identification of variants that lack mitogenic activity yet retain high affinity receptor binding. The EMBO journal 1992:11: 2503-2510

22. Gherardi E, Youles ME, Miguel RN et al. Functional map and domain structure of MET, the product of the c-met protooncogene and receptor for hepatocyte growth factor/scatter factor. Proceedings of the National Academy of Sciences of the United States of America 2003:100: 12039-12044

23. Park M, Dean M, Kaul K et al. Sequence of MET protooncogene cDNA has features characteristic of the tyrosine kinase family of growth-factor receptors. Proceedings of the National Academy of Sciences of the United States of America 1987: 84: 6379-6383

24. Di Renzo MF, Narsimhan RP, Olivero M et al. Expression of the Met/HGF receptor in normal and neoplastic human tissues. Oncogene 1991:6: 1997-2003

25. Birchmeier C, Gherardi E. Developmental roles of HGF/SF and its receptor, the c-Met tyrosine kinase. Trends in cell biology 1998:8: 404-410

26. Sachs M, Brohmann H, Zechner D et al. Essential role of Gab1 for signaling by the c-Met receptor in vivo. The Journal of cell biology 2000:150: 1375-1384

27. Sonnenberg E, Weidner KM, Birchmeier C. Expression of the met-receptor and its ligand, HGF-SF during mouse embryogenesis. Exs 1993:65: 381-394

28. Michalopoulos GK, DeFrances MC.Liver regeneration. Science ,New York, NY 1997:276: 60-66

29. Rong S, Segal S, Anver M et al. Invasiveness and metastasis of NIH 3T3 cells induced by Met-hepatocyte growth factor/scatter factor autocrine stimulation. Proceedings of the National Academy of Sciences of the United States of America 1994:91: 4731-4735

30. Laterra J, Nam M, Rosen E et al.Scatter factor/hepatocyte growth factor gene transfer enhances glioma growth and angiogenesis in vivo. Lab Invest 1997:76: 565-577

31. Abounader R, Lal B, Luddy C et al. In vivo targeting of SF/HGF and c-met expression via U1snRNA/ribozymes inhibits glioma growth and angiogenesis and promotes apoptosis. Faseb J 2002:16: 108-110

32. Kuniyasu H, Yasui W, Kitadai Y et al. Frequent amplification of the c-met gene in scirrhous type stomach cancer. Biochemical and biophysical research communications 1992:189: 227-232

33. Muleris M, Almeida A, Dutrillaux AM et al. Oncogene amplification in human gliomas: a molecular cytogenetic analysis. Oncogene 1994: 9: 2717-2722

34. Danilkovitch-Miagkova A, Zbar B. Dysregulation of Met receptor tyrosine kinase activity in invasive tumors. The Journal of clinical investigation 2002: 109: 863-867

35. Engelman JA, Zejnullahu K, Mitsudomi T et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science (New York, NY) 2007: 316: 1039-1043

36. Lamszus K, Schmidt NO, Jin L et al. Scatter factor promotes motility of human glioma and neuromicrovascular endothelial cells. International journal of cancer 1998:75: 19-28

37. Rosen EM, Laterra J, Joseph A et al. Scatter factor expression and regulation in human glial tumors. International journal of cancer 1996: 67: 248-255

38. Arrieta O, Garcia E, Guevara P et al. Hepatocyte growth factor is associated with poor prognosis of malignant gliomas and is a predictor for recurrence of meningioma. Cancer 2002: 94: 3210-3218

39. Bowers DC, Fan S, Walter KA et al. Scatter factor/hepatocyte growth factor protects against cytotoxic death in human glioblastoma via phosphatidylinositol 3-kinase- and AKT-dependent pathways. Cancer Res 2000; 2002:60: 4277-4283

40. Abounader R, Ranganathan S, Lal B et al. Reversion of human glioblastoma malignancy by U1 small nuclear RNA/ribozyme targeting of scatter factor/hepatocyte growth factor and c-met expression. J Natl Cancer Inst 1999: 91: 1548-1556

41. Laterra J, Rosen E, Nam M et al. Scatter factor/hepatocyte growth factor expression enhances human glioblastoma tumorigenicity and growth. Biochem Biophys Res Commun 1997:235: 743-747

42. Christensen JG, Schreck R, Burrows J et al. A selective small molecule inhibitor of c-Met kinase inhibits c-Met-dependent phenotypes in vitro and exhibits cytoreductive antitumor activity in vivo. Cancer research 2003: 63: 7345-7355

43. Halatsch ME, Schmidt U, Behnke-Mursch J et al. Epidermal growth factor receptor inhibition for the treatment of glioblastoma multiforme and other malignant brain tumours. Cancer treatment reviews 2006:32: 74-89

44. Karpel-Massler G, Schmidt U, Unterberg A et al. Therapeutic inhibition of the epidermal growth factor receptor in high-grade gliomas: where do we stand? Molecular cancer research : MCR 7: 2009 1000-1012

45. Berthou S, Aebersold DM, Schmidt LS et al. The Met kinase inhibitor SU11274 exhibits a selective inhibition pattern toward different receptor mutated variants. Oncogene 2004: 23: 5387-5393

46. Ma PC, Schaefer E, Christensen JG et al. A selective small molecule c-MET Inhibitor, PHA665752, cooperates with rapamycin. Clin Cancer Res 2005: 11: 2312-2319

47. Stommel JM, Kimmelman AC, Ying H et al. Coactivation of receptor tyrosine kinases affects the response of tumor cells to targeted therapies. Science 2007:318: 287-290

48. Kim KJ, Wang L, Su YC et al. Systemic anti-hepatocyte growth factor monoclonal antibody therapy induces the regression of intracranial glioma xenografts. Clin Cancer Res 2006: 12: 1292-1298

49. Burgess T, Coxon A, Meyer S et al. Fully human monoclonal antibodies to hepatocyte growth factor with therapeutic potential against hepatocyte growth factor/c-Met-dependent human tumors. Cancer research 2006:66: 1721-1729

50. Ekstrand AJ, Sugawa N, James CD et al. Amplified and rearranged epidermal growth factor receptor genes in human glioblastomas reveal deletions of sequences encoding portions of the – and/or C-terminal tails. Proceedings of the National Academy of Sciences of the United States of America 1992:89: 4309-4313

51. Sugawa N, Ekstrand AJ, James CD et al. Identical splicing of aberrant epidermal growth factor receptor transcripts from amplified rearranged genes in human glioblastomas. Proceedings of the National Academy of Sciences of the United States of America 1990: 87: 8602-8606

52. Wong AJ, Bigner SH, Bigner DD et al. Increased expression of the epidermal growth factor receptor gene in malignant gliomas is invariably associated with gene amplification. Proceedings of the National Academy of Sciences of the United States of America 1987: 84: 6899-6903

53. Li J, Yen C, Liaw D et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 1997:275: 1943-1947

54. Wang SI, Puc J, Li J et al. Somatic mutations of PTEN in glioblastoma multiforme. Cancer Res 1997: 57: 4183-4186

55. Lal B, Goodwin CR, Sang Y et al. EGFRvIII and c-Met pathway inhibitors synergize against PTEN-null/EGFRvIII+glioblastoma xenografts. Molecular cancer therapeutics 2009: 8: 1751-1760

56. Greenall SA, Donoghue JF, Van Sinderen M et al. EGFRvIII-mediated transactivation of receptor tyrosine kinases in glioma: mechanism and therapeutic implications. Oncogene 2015:10.1038/onc.2014.448