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FoxM1: a potential drug target for glioma

Yu Li¹, Sicong Zhang¹, and Suyun Huang^{1,2}

¹Department of Neurosurgery, the University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

Abstract

Malignant glioma is an aggressive disease and there is no effective therapy. Recently, with the elucidation of mechanisms for glioma formation and progression, the critical molecules involved in the process are considered as therapeutic targets and numerous of drugs against these targets are ongoing for evaluation in clinic trial. FoxM1 has been recognized as one of the common pathways in cancer cells including glioma cells. FoxM1 signal network is reported to be critical in glioma by promoting cell proliferation, invasion, angiogenesis and cancer stem cell self-renewal. FoxM1 may represent a novel therapeutic target and FoxM1 inhibitors may provide a new therapeutic strategy against glioma.

Keywords

FoxM1; glioma; proliferation; invasion; angiogenesis; self-renewal; drug target

New drug targets in malignant gliomas are aberrant molecules

Despite the pathological and genetic heterogeneity, the malignant gliomas share common molecular alterations with other cancers. The molecules acting on proliferation, avoidance of apoptosis, invasion and forming new blood vessels in other cancers play the same roles on glioma. Therefore, drug targets in other cancers can also be applied in malignant gliomas.

The epidermal growth factor receptor (EGFR) is overexpressed in gliomas and accompanied with the mutant EGFRvIII, which has a deletion of Exons 2–7 within the EGFR extracellular domain resulting in constitutive activation of EGFR signaling in ligand-independent manner. Thus, EGFR is considered as a molecular target in glioma therapy. Growth of malignant glioma is also dependent on angiogenesis which is mediated by vascular endothelial growth factor (VEGF) and other angiogenic factors. Bevacizumab (Avastin), a humanized neutralizing monoclonal antibody to VEGF has been approved by FDA to be as a therapeutic reagent for malignant glioma[1]. The malignant glioma often has aberrant activation of signal transduction pathway, such as RAS/RAF/MEK and PI3K/AKT/mTOR pathways. Thus the key intracellular effectors activated in the two pathways are evaluated as drug targets. For example, Rapamycin, an inhibitor of mTOR and its synthesized analogs, temsirolimus, everolimus, and AP23573 have been evaluated in clinical trials of malignant gliomas[2].

² Author for correspondence: Phone: 713-834-6232; Fax: 713-834-6257; suhuang@mdanderson.org.

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The critical roles of FoxM1 in malignant gliomas highlight its potential as a drug target

Forkhead box protein M1 is a member of the Fox family of transcription factors. The human *FoxM1* gene is composed of 10 exons of which two are alternatively spliced. These splice events give rise to three different splice variants named FoxM1a, -b and -c. FoxM1a has been shown to be a transcriptional repressor whereas FoxM1b and FoxM1c are both transcriptional activators[3].

FoxM1 expression is gradually increasing from G0-phase and reaches peak in late G1 or early S-phase. The protein levels of FoxM1 are sustained until the end of G2-phase and then it rapidly decreases during the mitosis. The altered expression accompanied with cell cycle transition highlights that the major function of FoxM1 is in regulation of cell cycle. It has been reported that FoxM1 plays an important role on regulating the transition from G1 to S phase and G2 to M phase in cell cycle progression. FoxM1 induces expression of cyclin A2, JNK1, ATF2, Cdc25A phosphatase and inhibits the stability of p21Cip1 and p27Kip1 proteins to regulate G1/S transition and DNA replication[4]. FoxM1 also regulates expression of a large array of G2/M-specific genes, such as *CDC25B*, *AURKB*, *PLK1*, *CENPA*, *CENPB*, *CENPF*, *BIRC5* and cyclin B [5]. Depletion of FoxM1 in cells results in G2 phase delays and severe mitotic abnormalities that lead to dysfunction of chromosomal segregation and genomic instability.

FoxM1 gene is now known as a human proto-oncogene[6]. Upregulation of FoxM1 is involved in many cancers such as skin, liver, breast, lung, prostate, colon, pancreas, ovarian and brain[7]. FoxM1 and its regulated genes such as *AURKB*, *CCNB1*, *BIRC5*, *CDC25* and *PLK1*, were consistently overexpressed and the signal molecules are significantly activated in tumours compared to adjacent epithelial tissue[8].

In a previous study [9], we determined the expression of FoxM1 in normal brain and glioma with different grades. No positive staining was detected in normal brain tissues. In gliomas, only 4% of the low-grade astrocytomas (1 of 25 tumors) were strongly positive, 4% were moderately positive, and 92% were negative. 14.7% of the anaplastic astrocytomas were strongly positive, 26.5% were moderately positive, and 58.8% were negative for FoxM1 expression. As for glioblastoma multiformes, 36% were strongly positive, 36% were moderately positive, and 28% were negative for FoxM1 expression. Our study showed FoxM1 expression in the human glioma tissues is apparently higher than that in normal tissue and this expression is directly correlated to the grade of the glioma. Our study also showed increased expression of FoxM1 in glioblastoma multiforme was significantly associated with poor overall survival of patients. Further, FoxM1 was found to regulate expression of Skp2 protein which promotes degradation of p27Kip1, resulting in aberrant cell cycle and glioma tumorigenicity.

Besides regulation of cell cycle, FoxM1 promotes glioma angiogenesis through the up-regulation of VEGF expression. FoxM1 transactivates VEGF through direct binding to the *VEGF* gene promoter[10]. FoxM1 protein also binds directly to *MMP2* promoter and increases MMP-2 expression[11]. MMP-2 plays an important role in cancer invasion through basement membrane degradation. Thus, FoxM1 contributes to glioma invasion by promoting *MMP2* gene transcription. FoxM1 not only acts as a direct transcriptional regulator but exerts other functions by interaction with other proteins. FoxM1 recently was reported to bind directly to β -catenin and enhances β -catenin nuclear localization and transcriptional activity[12]. Further, FoxM1 enhances its functions on self-renewal of glioma stem cells and on driving glioma formation by interaction with β -catenin.

The small molecular inhibitor against FoxM1 is a promising therapy strategy for glioma

FoxM1 has two essential characters which make it druggable in gliomas: overexpression in gliomas and the ability to enhance activity in carcinogenesis and progression. Therefore, FoxM1 inhibitors are expected to be druggable in the future therapy of gliomas. The first anti-FoxM1 inhibitor is a 26–44 peptide of p19ARF. p19ARF proteins are induced in cancer initiation and exert cancer inhibition function by increase stability of the p53 tumor suppressor. The minimal efficient version of p19ARF is a 26–44 peptide containing nine D-Arg, which can significantly reduce FoxM1 transcriptional activity and FoxM1-induced growth of cancer cells[13].

The first small molecular inhibitor against FoxM1 is Siomycin A which is obtained by screening a compound pool. Siomycin A can both reduce FoxM1 expression and blocking its phosphorylation to reduced its transactivation ability[14]. A dose dependent decrease of FoxM1 transcriptional activity was observed after Siomycin A treatment, along with reduced FoxM1 targeting survivin expression and Cdc25B and CENPB transcripts[14]. Moreover, Siomycin A treatment decreases protein and mRNA levels of FoxM1 and selectively inhibits anchorage-independent growth in transformed but not normal fibroblasts by inducing apoptosis. A later study shows Siomycin A is efficacious to suppress breast cancer in a xenograft mouse model[15]. Recent studies also show that Siomycin A can suppress brain tumor growth[16, 17]. Priller and co-workers demonstrate Siomycin A significantly inhibits medulloblastoma growth in vitro[16]. They suggested FoxM1 as a novel target for medulloblastoma treatment and Siomycin A as a drug candidate which recapitulates effects of FoxM1 knockdown in mitotic catastrophe and growth inhibition[16]. A more detailed research on anticancer activity of Siomycin A in brain tumor was presented by Nakano et al[17]. They demonstrated that Siomycin A treatment preferentially inhibits stemlike Glioblastoma multiforme (GBM) cells growth through apoptosis and inhibition of self-renewal. Further, Siomycin A pretreatment yielded abraded size of stem-cell derived tumor and intratumoral injection of Siomycin A prolonged the survival of mice harboring intracranial tumors, supporting its antitumor activity in vivo. In line with previous studies showing little toxicity of Siomycin A to normal fibroblasts and HEK293T [14, 16], their study also indicated Siomycin A has little effect to normal cells. These data encouragingly reveal a potential drug candidate in targeted therapy in brain tumor.

Siomycin A belongs to a class of thiopeptide antibiotics, which are characterized by sulfur-containing heterocyclic rings. Thiostrepton is a similar natural thiopeptide antibiotics as Siomycin A. It is also reported to represent a specific inhibitor of FoxM1[18] and possess anticancer activity[19]. Likewise, thiostrepton decreases FoxM1 protein and mRNA levels thus conferring to apoptosis and reduced cell migration, invasiveness, and transformation in breast cancer cells [18]. In addition to the intuitive mechanism of decreased FoxM1 downstream transcripts resulting from decreased FoxM1 protein, Balasubramanian's group provided a novel model elucidating reduced FoxM1 transcriptional activity effected by thiostrepton[20]. They showed that through its direct binding to FoxM1, thiostrepton blocks FoxM1 binding to the promoter/enhancer region of downstream target genes in the breast tumor cells even when FoxM1 protein levels only slightly decreased within four hours of thiostrepton exposure. Taken together, the emerging thiopeptide antibiotics are attractive potential anticancer drugs in brain tumor treatment.

Future perspective

FoxM1 plays important roles in glioma formation and progression, thus it is a potential drug target for glioma therapy. However, FoxM1 inhibitors have not yet been entered into clinical

trials. There is a need for more thorough preclinical studies on their anti-tumor efficacy. Although FoxM1 inhibitors may exert little toxicity to normal fibroblasts and brain cells, it is unknown if FoxM1 inhibitors have side effects in patients. The toxicity and side effects of FoxM1 inhibitors must be thoroughly investigated in animal models and ultimately in clinical trials. It is also expected that more FoxM1 small molecule inhibitors will emerge, and some of them may be permeable for blood-brain barrier, hence have more advantage in glioma treatment. Nevertheless, given the critical role of FoxM1 in regulating the multiple steps of glioma formation and progression, targeting of FoxM1 may prove to be a more effective approach to control glioma than merely targeting individual molecules, such as VEGF. Thus, targeting FoxM1 may represent a novel approach to treat malignant glioma.

References

1. Friedman, Hs; Prados, Md; Wen, Py, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* 2009; 27(28):4733–4740. [PubMed: 19720927]
2. Sathornsumetee S, Reardon Da, Desjardins A, Quinn Ja, Vredenburgh Jj, Rich Jn. Molecularly targeted therapy for malignant glioma. *Cancer.* 2007; 110(1):13–24. [PubMed: 17520692]
3. Koo, Cy; Muir, Kw; Lam, Ew. FOXM1: From cancer initiation to progression and treatment. *Biochim Biophys Acta.* 2011; 1819(1):28–37. [PubMed: 21978825]
4. Wang, Ic; Chen, Yj; Hughes, D., et al. Forkhead box M1 regulates the transcriptional network of genes essential for mitotic progression and genes encoding the SCF (Skp2-Cks1) ubiquitin ligase. *Mol Cell Biol.* 2005; 25(24):10875–10894. [PubMed: 16314512]
5. Laoukili J, Kooistra Mr, Bras A, et al. FoxM1 is required for execution of the mitotic programme and chromosome stability. *Nat Cell Biol.* 2005; 7(2):126–136. [PubMed: 15654331]
6. Myatt, Ss; Lam, Ewf. The emerging roles of forkhead box (Fox) proteins in cancer. *Nature Reviews Cancer.* 2007; 7(11):847–859.
7. Wang Z, Ahmad A, Li Y, Banerjee S, Kong D, Sarkar Fh. Forkhead box M1 transcription factor: a novel target for cancer therapy. *Cancer Treat Rev.* 2010; 36(2):151–156. [PubMed: 20022709]
8. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011; 474(7353):609–615. [PubMed: 21720365]
9. Liu M, Dai B, Kang Sh, et al. FoxM1B is overexpressed in human glioblastomas and critically regulates the tumorigenicity of glioma cells. *Cancer Res.* 2006; 66(7):3593–3602. [PubMed: 16585184]
10. Zhang Y, Zhang N, Dai B, et al. FoxM1B transcriptionally regulates vascular endothelial growth factor expression and promotes the angiogenesis and growth of glioma cells. *Cancer Res.* 2008; 68(21):8733–8742. [PubMed: 18974115]
11. Dai B, Kang Sh, Gong W, et al. Aberrant FoxM1B expression increases matrix metalloproteinase-2 transcription and enhances the invasion of glioma cells. *Oncogene.* 2007; 26(42):6212–6219. [PubMed: 17404569]
12. Zhang N, Wei P, Gong A, et al. FoxM1 promotes beta-catenin nuclear localization and controls Wnt target-gene expression and glioma tumorigenesis. *Cancer Cell.* 2011; 20(4):427–442. [PubMed: 22014570]
13. Kalinichenko, Vv; Major, Ml; Wang, X., et al. Foxm1b transcription factor is essential for development of hepatocellular carcinomas and is negatively regulated by the p19ARF tumor suppressor. *Genes Dev.* 2004; 18(7):830–850. [PubMed: 15082532]
14. Radhakrishnan, Sk; Bhat, Ug; Hughes, De; Wang, I-C.; Costa, Rh; Gartel, Al. Identification of a Chemical Inhibitor of the Oncogenic Transcription Factor Forkhead Box M1. *Cancer Res.* 2006; 66(19):9731–9735. [PubMed: 17018632]
15. Halasi M, Zhao H, Dahari H, et al. Thiazole antibiotics against breast cancer. *Cell Cycle.* 2010; 9(6):1214–1217. [PubMed: 20410687]
16. Priller M, Pöschl J, Abrão L, et al. Expression of FoxM1 Is Required for the Proliferation of Medulloblastoma Cells and Indicates Worse Survival of Patients. *Clinical Cancer Research.* 2011; 17(21):6791–6801. [PubMed: 21918172]

17. Nakano I, Joshi K, Visnyei K, et al. Siomycin A targets brain tumor stem cells partially through a MELK-mediated pathway. *Neuro-Oncology*. 2011; 13(6):622–634. [PubMed: 21558073]
18. Kwok, Jm; Myatt, Ss; Marson, Cm; Coombes, Rc; Constantinidou, D.; Lam, Ew. Thiostrepton selectively targets breast cancer cells through inhibition of forkhead box M1 expression. *Mol Cancer Ther*. 2008; 7(7):2022–2032. [PubMed: 18645012]
19. Nicolaou, Kc; Zak, M.; Rahimipour, S., et al. Discovery of a biologically active thiostrepton fragment. *J Am Chem Soc*. 2005; 127(43):15042–15044. [PubMed: 16248640]
20. Hegde, Ns; Sanders, Da; Rodriguez, R.; Balasubramanian, S. The transcription factor FOXM1 is a cellular target of the natural product thiostrepton. *Nat Chem*. 2011; 3(9):725–731. [PubMed: 21860463]