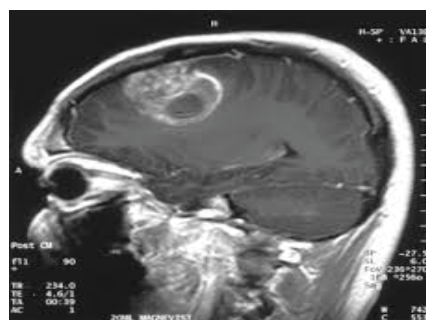


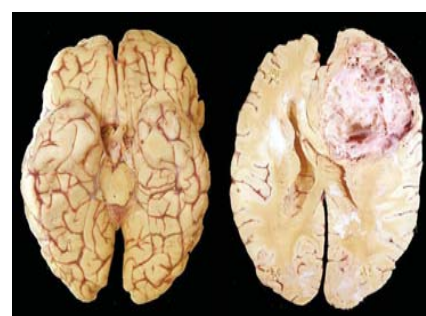
The transcriptional modulator HMGA2 promotes glioblastoma invasion and tumorigenicity

Abstract

Glioblastoma (GBM) is a highly invasive and devastating brain tumor with no curative treatments. GBM contains a small subpopulation of tumor stem-like cells believed to be highly invasive and resistant to therapies. Discovering novel molecular targets regulating tumor stemness and developing therapies is urgently needed to improve patient outcomes. Our group has previously shown that the developmentally important LIN28A pathway regulates the stem cell factor HMGA2 in GBM. HMGA2 is highly expressed in normal and cancer stem cells. Elevated levels of HMGA2 in tumors is associated with increased stemness and invasion. We found that HMGA2 is highly expressed in majority of GBM tumors and patient-derived GBM cell lines compared to normal brain. Short-hairpin RNA (shRNA) mediated reduction of HMGA2 decreased GBM cell invasion and clonogenicity in vitro. Importantly, knockdown of HMGA2 using shRNA decreased GBM tumor formation in intracranial xenografts in immunocompromised mice. Our data suggests that HMGA2 is a viable therapeutic target in GBM. Future studies will focus on identifying the molecular mechanisms downstream of HMGA2.



https://en.wikipedia.org/wiki/Glioblastoma_multiforme



<https://biomnews-tx.com/news/news-tags/glioblastoma/>

Introduction

- Glioblastoma (GBM) is a grade four astrocytoma (tumors that arise from astrocytes) with poor prognosis, as there is no curative treatments. They are highly invasive.
- Various stem cells factors have been shown to be important in tumors, one such factor is called Lin28A. It has been shown previously by Dr. Raabe to be key contributor in glioblastoma tumorigenesis.
- Lin28A negatively regulates microRNA Let 7 and further Let 7 negatively regulates another stem cell factor called HMGA2.
- In this way, Lin28A promotes the expression of HMGA2. HMGA2 also known as High Mobility Group AT hook 2 binds to DNA and act as a transcriptional regulating factor.
- HMGA2 is highly expressed during fetal development but not in normal adult tissues.
- Elevated levels of HMGA2 in different tumors promote invasion, stemness, and tumor growth. Its significance is not yet studied in GBM.

Results

Expression of HMGA2 in GBM tumors and cell lines

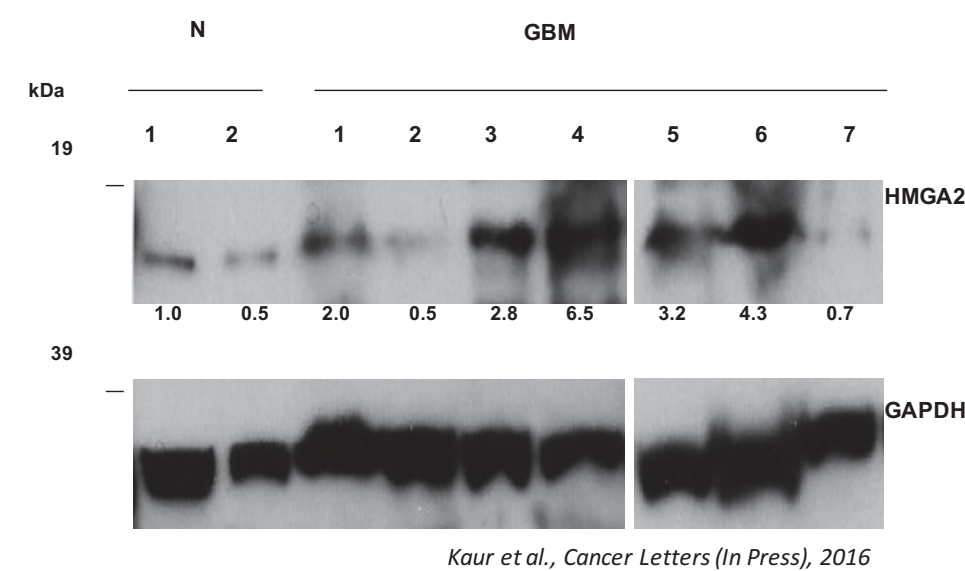


Figure 1 (above)¹: Levels of HMGA2 are shown in various different GBM cell lines. Based on the result, HMGA2 expression is relatively higher in GBM cells compared to normal non-GBM cells. GAPDH is used as indicator of protein levels.

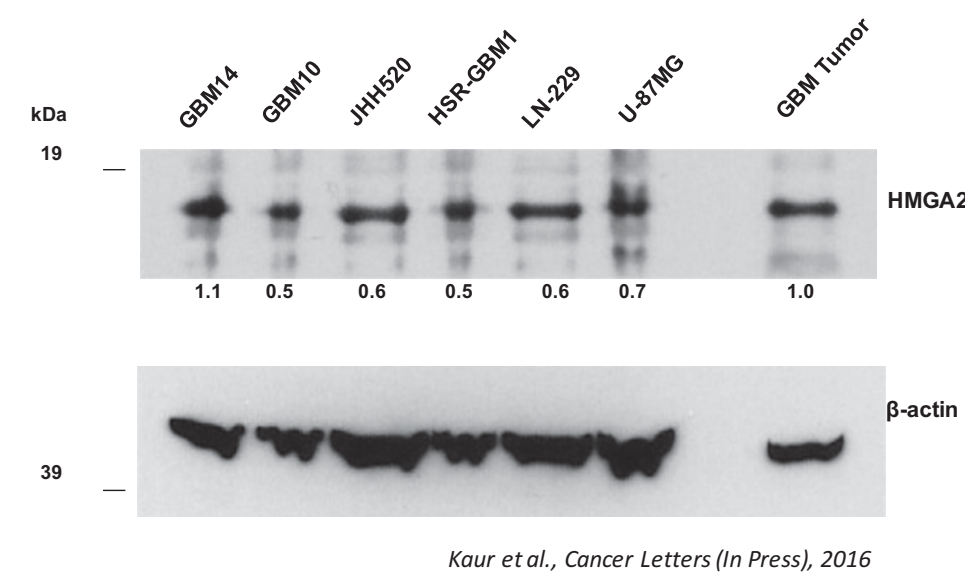


Figure 2 (above)¹: The western blot above shows that protein HMGA2 is highly expressed in different cells obtained from different patients with GBM.

Knockdown inhibits invasion and clonogenicity

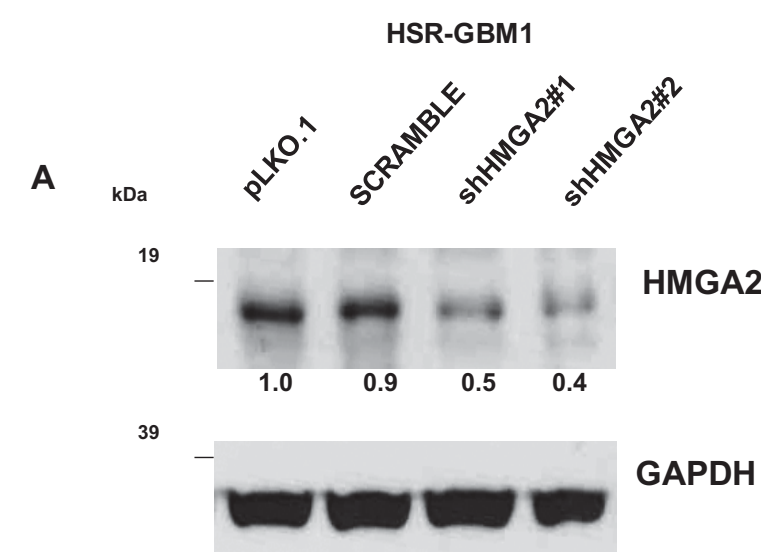


Figure 5 (above)¹: (a) Various different shHMGA2 were used to target HMGA2. shHMGA2 #2 knocked down the HMGA2 much more effectively. (b) The present average number of colonies of cells with shHMGA2 was significantly lower than the control. (c.) The number of cell invasion decreases in cell lines with shHMGA2.

Knockdown inhibits tumorigenicity

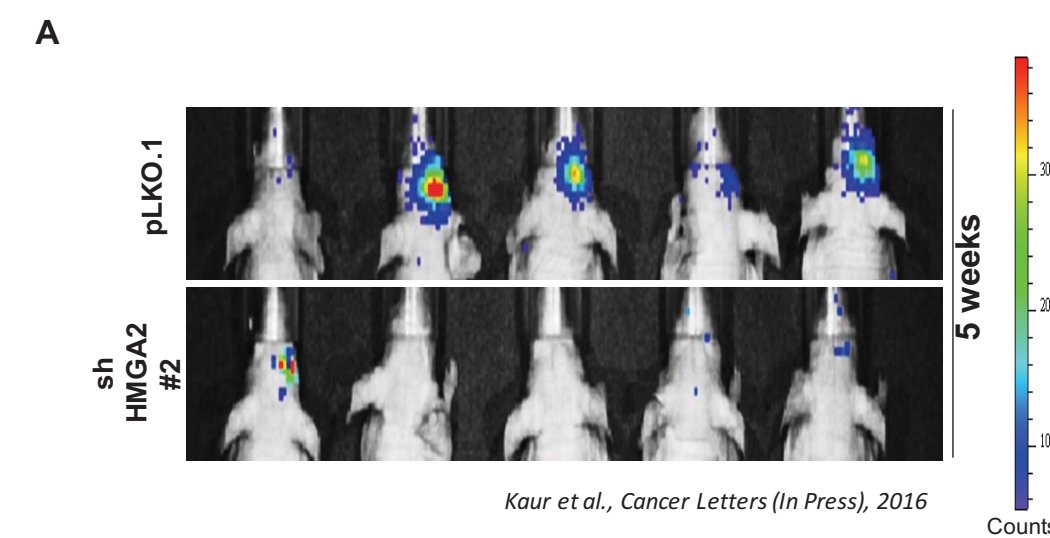


Figure 3 (above)¹: Progression of GBM tumor in mice in span of five weeks. When HMGA2 was inhibited by shHMGA2, the invasion and clonogenicity properties of GBM diminished.

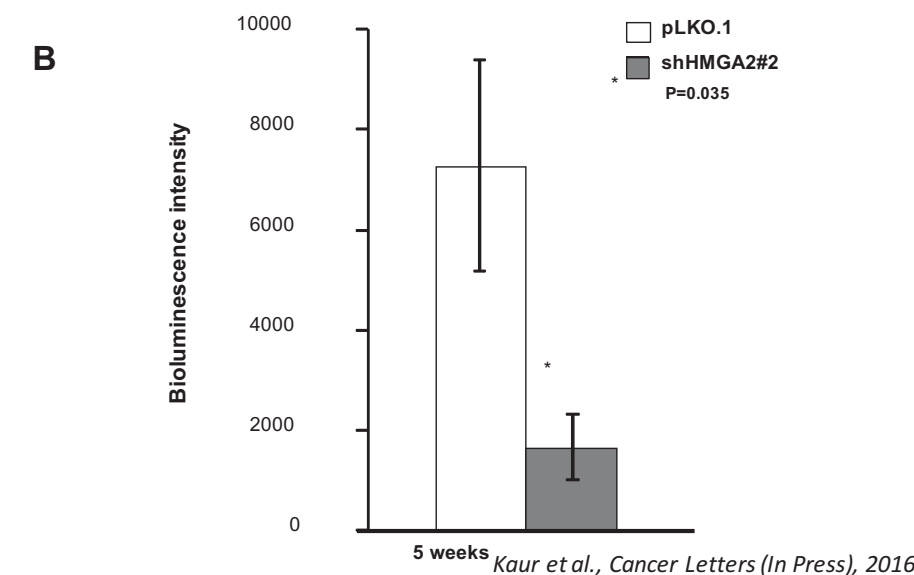
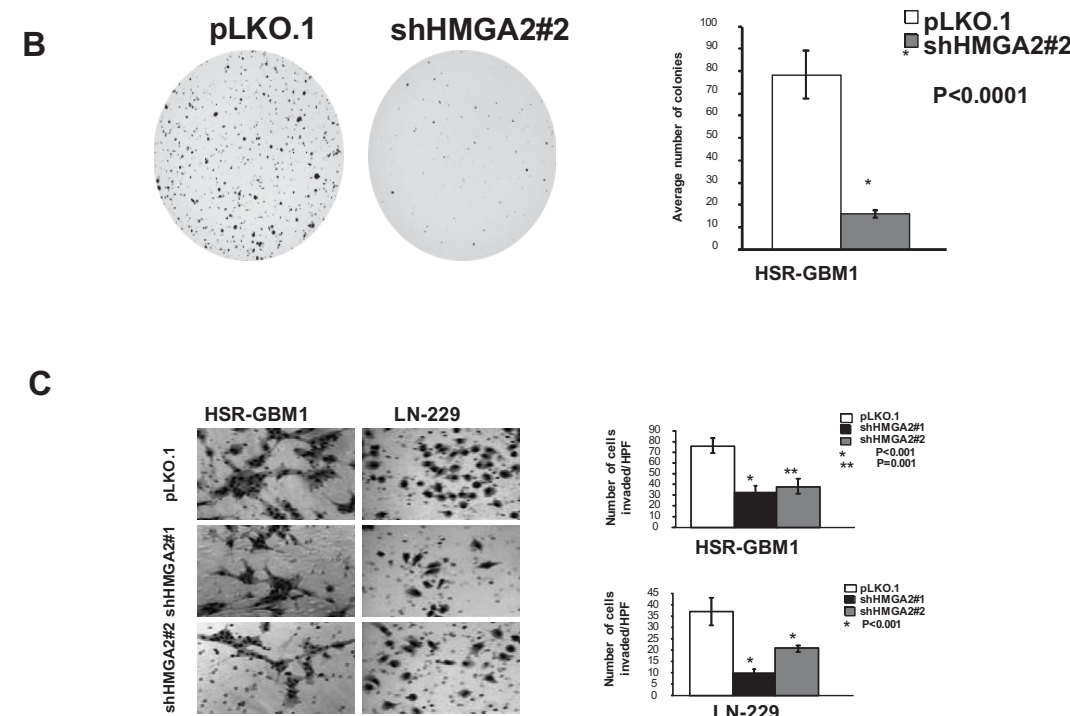


Figure 4 (above)¹: Bioluminescence intensity data illustrating the intensity of tumor in Figure 3.



Kaur et al., Cancer Letters (In Press), 2016

Conclusion

- Glioblastoma is a non curative cancer. We found that HMGA2 promotes glioblastoma invasion and tumorigenicity.
 - Our group has previously shown that LIN28A pathway regulates the stem cell factor HMGA2.
- Lin28A —| Let 7 —| HMGA2
- HMGA2 is highly expressed in GBM.
 - Knockdown of HMGA2 lowered the invasion and clonogenicity of the tumor significantly.
 - Knockdown of HMGA2 also inhibited tumorigenicity.

Future Directions

- Focus on why HMGA2 is highly expressed in GBM tumors
- Identify any downstream effects of elevated levels of HMGA2

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LIN28A facilitates the transformation of human neural stem cells and promotes glioblastoma tumorigenesis through a pro-invasive genetic program
Xing-gang Mao,^{1,2} Marianne Hütt-Cabezas,¹ Brent A. Orr,¹ Melanie Weingart,¹ Isabella Taylor,¹ Anand K.D. Rajan,¹ Yazmin Odia,^{3,4} Ulf Kahlert,¹ Jarek Maciaczyk,^{5,6} Guido Nikkha,^{7,8} Charles G. Eberhart,¹ and Eric H. Raabe^{1,9}
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