The transcriptional modulator HMGA2 promotes glioblastoma invasion and tumorigenicity

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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.

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.

Expression of HMGA2 in GBM tumors and cell lines

Knockdown inhibits invasion and clonogenicity

Knockdown inhibits tumorigenicity

Future Directions

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

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.

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References

LIN28A facilitates the transformation of human neural stem cells and promotes glioblastoma tumorigenesis through a pro-invasive genetic program
Xing-jiang Mao, 1, 2, Marianne Hütt-Cabezas, 1, 2, Brent A. Orr, 1, Melanie Weingart, 1, Isabella Taylor, 1, Anand K.D. Rajan, 1, Yezmin Oda, 1, 2, Uff Kahler, 1, Jarek Maciack, 2, 3, Guido Nikkhah, 3, 4, Charles G. Eberhart, 3, 1, and Eric H. Raabe 1, 2, 2.

2.) The transcriptional modulator HMGA2 promotes stemness and tumorigenicity in glioblastoma.