Exploring the role of FKBP38 in glioblastoma immune response

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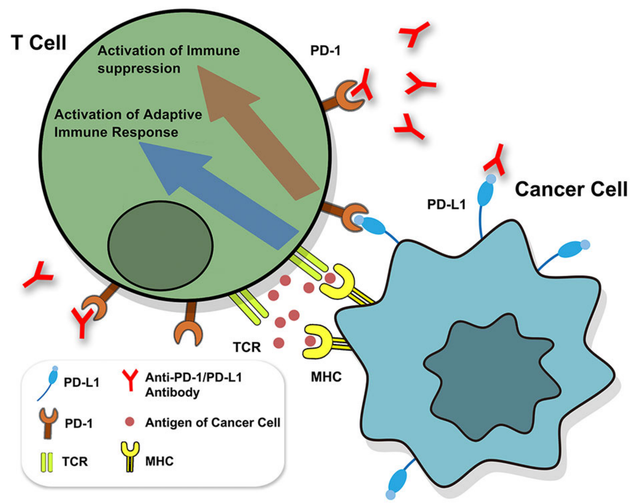
Abstract/Introduction

Background: Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor. Multimodal standard care consists of surgical resection followed by radiation and chemotherapy. However, prognosis for GBM patients remains grim, with a median overall survival of 14 months. Currently, novel molecular therapeutic targets are being explored for GBM. FKBP38 is a multidomain immunophilin protein that plays an important role in the regulation of cellular functions like apoptosis and autophagy. FKBP38 is upregulated in GBM primary neurospheres (GBMNS) and its knockdown increases GBMNS autophagy, decreases GBMNS viability, and extends the survival of tumor-bearing mice. In this study we tested if FKBP38 regulates immune response in the GBM tumor microenvironment. Initial unbiased screening for cytokine/chemokines showed significant change in chemokines such as GDF-15 and EGF. GDF-15 and EGF are known to positively regulate and stabilize PDL-1. Hence, we probed for the expression of PDL-1 and its upstream target IL-6. Expression of IL-6 and PDL-1 reduces with FKBP38 depletion, suggesting a potential role for FKBP38 in regulating the GBM immune response.



Objective

To study the role of FKBP38 and its inhibition of the immune response in GBM.

FKBP38 Expression in GBMNS

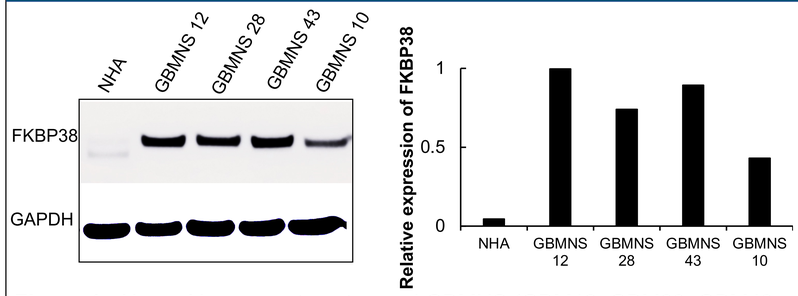


Figure 1: Normal human astrocytes and GBMNS (GBM12, GBM28, GBM43, GBM10) were probed for FKBP38 expression by western blot.

FKBP38 knockdown decreases the viability of GBMNS through autophagy

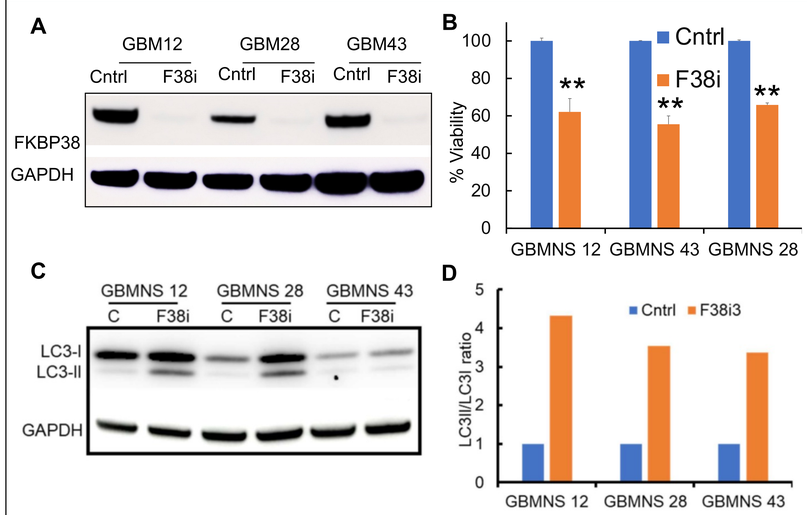


Figure 2: GBMNS transfected with non-target siRNA (Cntrl) or FKBP38-target-specific siRNA (F38i) were A) validated for FKBP38 knockdown and C, D) probed for LC3-I and LC3-II expression by western blot. GBMNS transfected with or without FKBP38-depletion were subjected to B) viability assay.

FKBP38 knockdown extends the survival of tumor bearing mice

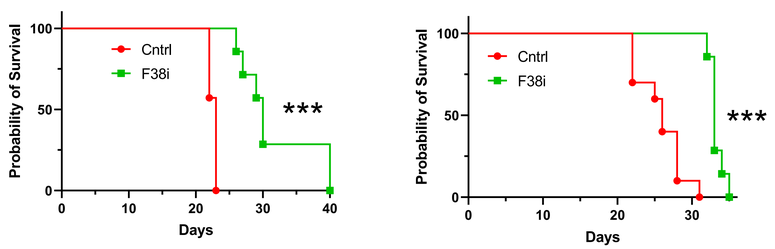


Figure 3: GBMNS transfected with Cntrl or F38i were implanted and the mice were followed for their survival. Graph represents the Kaplan-meier survival plot.

FKBP38 depletion reduces PD-L1 and IL-6 levels in GBMNS

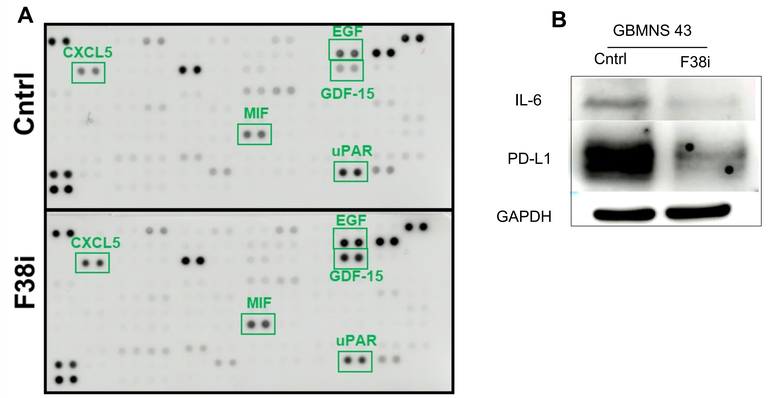


Figure 4: A) Antibody array showing changes in the cytokine/chemokine profile with F38i in comparison to control in GBMNS. B) GBMNS transfected with Cntrl or F38i were probed for IL-6 and PD-L1 expression by western blot analysis.

Conclusions

- FKBP38 depletion changes chemokine and cytokine profile of GBMNS
- FKBP38 knockdown reduces PDL-1 and IL-6 expression

Future Direction

- To probe the functional relevance of FKBP38-regulated chemokine and cytokine profile in the context of immune response in GBM tumor microenvironment in in vivo and in vitro GBM models

Acknowledgement

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References

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