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DRUG REPURPOSING SCREEN REVEALS GLIOBLASTOMA CELL LINE SUSCEPTIBILITY TO STATINS

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Introduction and aim

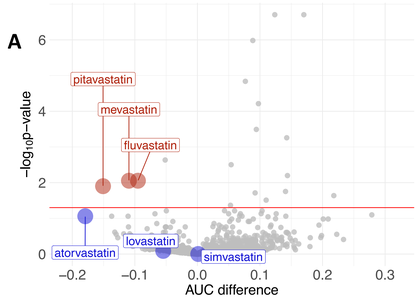
- Glioblastoma treatment consists mainly of tumor resection, radiotherapy, and temozolomide.
- Within the past decade, glioblastoma tumors have been extensively molecularly characterized, although this information has not been translated into increased patient survival.
- Many cancer cell lines have been functionally assessed with data being accessible to everyone.
- In this study we explored these open-source databases to explore drug susceptibilities in glioblastoma cell lines, elucidate the probable mechanism of action, and validate findings in spheroid cultures derived from glioblastoma patients.

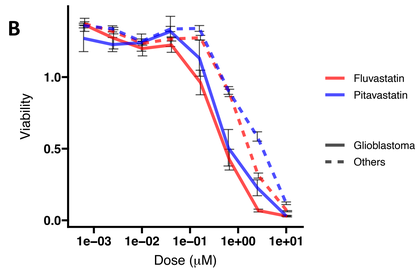
Methods

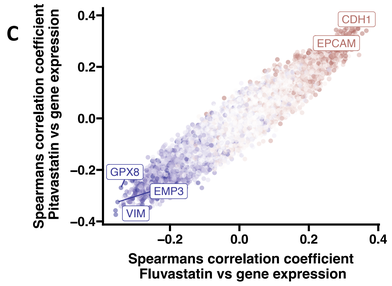
- We downloaded cell line data from The Cancer Dependency Map which includes datasets quantifying both mRNA expression levels and cell viability after drug exposure or genomic knockout.
- We identified potential drugs by t-testing cell viability after drug exposure between glioblastoma cell lines and cell lines from other cancer types.
- We performed multiple statistical methods to elucidate mechanism of action and biomarkers for susceptibility and assessed these markers in non-cultured glioblastoma cells and tumors.

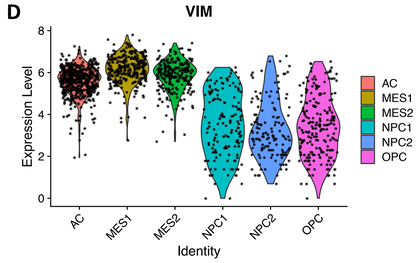
Results

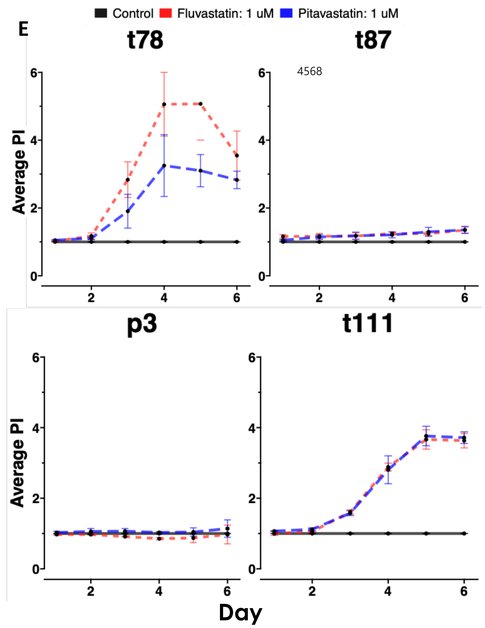
- A: T-testing over 1500 drugs reveals multiple statins to have significant effects in GBM cell lines compared to other cancers.
- B: Dose-response curves shows increased glioblastoma sensitivity to statins.
- C: Across cancer cell lines, the statin sensitivity is correlated with mesenchymal markers and inversely correlated with epithelial markers.
- D: Single-cell analysis on in silico data shows that some glioblastoma cell states have high expression of mesenchymal marker VIM.
- E: Patient-derived glioblastoma spheroid cultures were treated with statins, and mesenchymal cultures T78 and T111 showed sensitivity at 1uM.
- F: When correlating the effects of statins with genetic dependencies, the genetic dependency of UBIAD1 is most correlated to the effects of fluvastatin indicating that the mechanism of action occurs through it's direct or indirect inhibition.

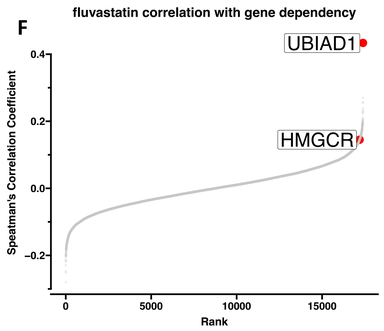


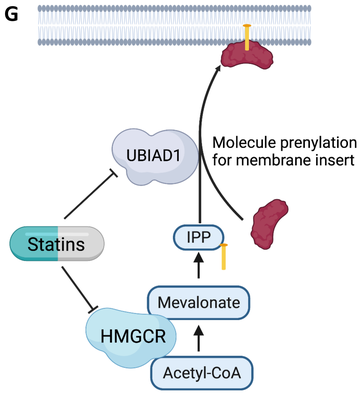












Discussion

- We propose that the anti-cancer effects of statins in glioblastoma cells may cause cell death by inhibiting UBIAD1 (Fig G).
- Targeting mesenchymal cancer cells with statins may synergize with other therapeutics.

Conclusion

- Glioblastoma cell lines are more susceptible to statins compared to other cancer cell lines.
- HMGCR is the known target of statins, although statin-induced cell death may be caused by the downstream inhibition of UBIAD1, an enzyme involved in prenylation.

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