Targeting Glioblastoma Cell Migration via Teratocarcinoma-Derived CRIPTO-Positive Extracellular Vesicles

14th 2026 SOCRATIC LECTURES

CNR | IGB

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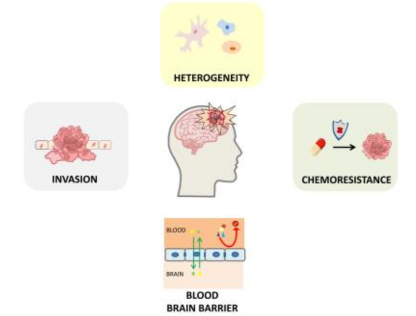
ABSTRACT

Glioblastoma (GB) is the most aggressive and lethal primary brain tumor, characterized by heterogeneity, invasiveness, and resistance to therapy. Its strong migratory capacity prevents complete surgical resection and promotes recurrence, making cell migration a key therapeutic target and a major barrier to survival (1,2). Extracellular vesicles (EVs) are lipid bilayer nanoparticles released by most cells. EVs carry proteins, nucleic acids, lipids, and metabolites, and they mediate intercellular communication in both physiological and pathological contexts, including GB (2). EVs from different donor cells can be applied to various recipient cells, highlighting their translational potential. Their ability to circulate in biological fluids and cross the blood–brain barrier makes them promising tools for brain cancer therapy. Tumor-derived EVs have attracted considerable attention as cancer-targeted therapeutic agents, both in immunotherapy and as drug delivery systems capable of efficiently transporting cargos to malignant cells (3). We reported for the first time the isolation and characterization of EVs from teratocarcinoma NTERA2 cells, which are neural progenitor-like cells able to locate, target and modulate GB cells. Notably, the 10,000x g fraction (medium/large EVs) exhibits an anti-migratory effect on GB cells, involving the EV-associated GPI-anchored protein CRIPTO, which plays a key role in both embryonic development and tumorigenesis (4). These findings have resulted in the granting of an Italian patent (IT202200007580, 2024), as well as the filing of European (EP4507714) and U.S. (US2025255983) patent applications. The anti-migratory effect is specific, and is not associated to uncontrolled proliferation, chemoresistance, or immune activation, supporting the exploitation of NTERA2-derived EVs for developing novel GB therapies.

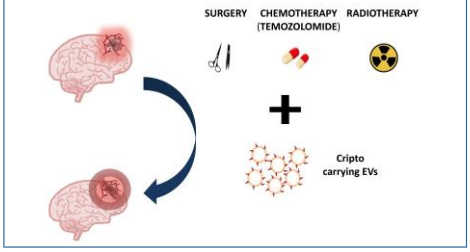
GLIOBLASTOMA OVERVIEW



Adapted from D'Antonio et al., Biology 2025

WORKING HYPOTHESIS

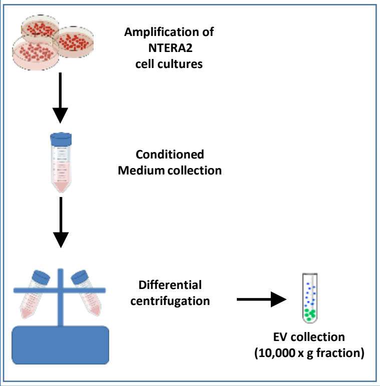
The delivery of CRIPTO via EVs might modulate GB progression, potentially reducing invasiveness and improving desease prognosis.



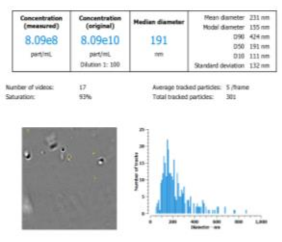
EXPERIMENTAL WORKFLOW

Isolation and Characterization of EVs → Functional studies to assess the efficacy and safety of EVs → Investigation of EV mechanism of action

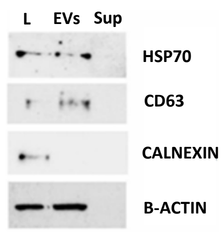
1. Isolation and Characterization of EVs



Myriade Analysis

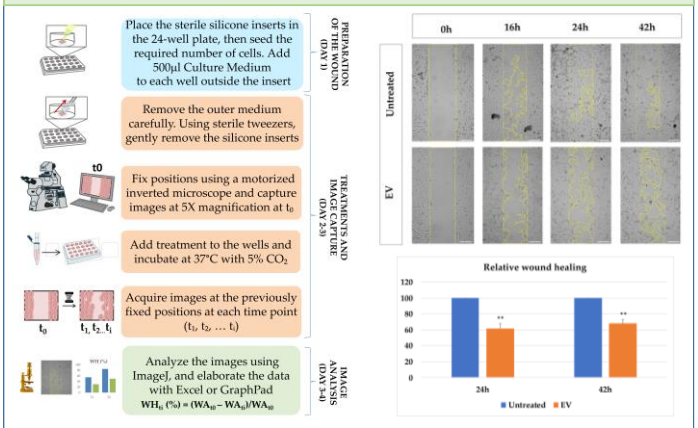


Western Blot Analysis



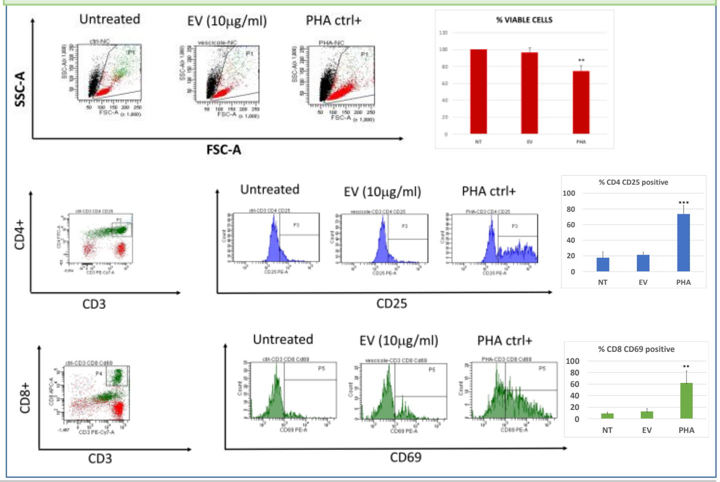
L: cell lysate;
Sup: supernatant

2. EV-Mediated Inhibition of GB Cell Migration in Wound Healing Assay

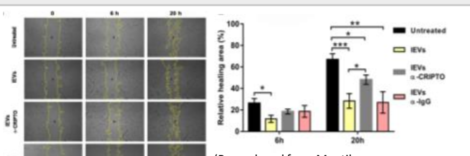


Adapted from manuscript under review (Methods and Protocols, MDPI)

3. EV Immune Tolerance in PBMCs

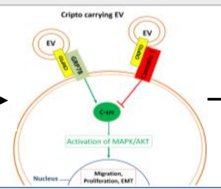


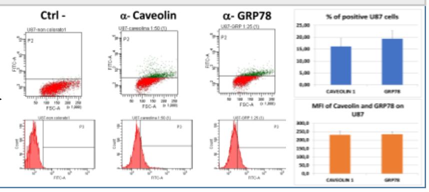
4. Involvement of EV-Associated Cripto and Putative Membrane Mediators in GB Cell Migration Inhibition



(Reproduced from Mantile et al., Cancers 2022)

Pre-incubation of EVs with an anti-CRIPTO antibody attenuates the anti-migratory effect on U87 GB cells, suggesting the involvement of CRIPTO in this process





CONCLUSIONS

EVs inhibit U87 GB cell migration without inducing immune cytotoxicity or T-cell activation. CRIPTO-related mediators (Caveolin-1 and GRP78), were foundt on the U87 cell membrane, and may underlie this antimigratory effect.

REFERENCES

(1)D'Antonio C. and Liguori G.L. (2025). *Biology* 14, 1490. DOI: 10.3390/biology14111490 (2)Liguori, G.L. (2024). *Cells* 13, 336. DOI: 10.3390/cells13040336. (3)Liguori G.L., Kralj-Iglič V. (2023). *Cancers (Basel). 15: 4425.* DOI: 10.3390/cancers15184425 (4)Mantile F., et al. DOI: 10.3390/cancers14153700.