The role of ICAM1 in glioblastoma tumor associated macrophages under hypoxia

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Introduction

Glioblastoma (GBM) is an aggressive and fatal brain cancer in adults with ineffective existing treatment methods (1). Cell adhesion molecules (CAMs) are proteins that are expressed on the surface of cells and enable them to communicate and interact with one another and the surrounding environment. They, in part, enable tumor cell invasion and migration (4). Intracellular adhesion molecule 1 (ICAM1) is a CAM expressed by TAMs in GBM (5). Tumor associated macrophages (TAMs) make up more than 40% of the GBM tumor mass and are thought to enhance tumor growth and proliferation, particularly within the characteristic hypoxic tumor microenvironment (TME) of GBM (6).

Objective/Hypothesis

Objective: My project aims to determine if ICAM1 expression in TAMs contributes to GBM tumorigenicity, uncover the mechanism of this behavior and if there are biological-sex related differences associated with its function in macrophages.

Hypothesis: I hypothesize that the expression of ICAM1 on the surface of TAMs contributes differently to male and female GBM cell invasiveness, especially in the hypoxic TME, by enhancing the interaction between tumor cells and macrophages, thereby facilitating the migration and invasion of the tumor cell.

Methods

Assess the expression levels of ICAM1 in primary and immortalized human and mouse macrophages under hypoxic conditions (1% O2, 0.2% O2, and HIF stabilizing drug IOX4). Analyze the effect of ICAM1 deficiency, knockdown, and overexpression and hypoxic conditions on macrophage behaviour including migration, proliferation, and adhesion to tumor cells. Intracranially inject ICAM1 deficient mouse model with GBM followed by analysis of tumor growth, overall survival and the composition of the tumor microenvironment.

Results

Conclusion

- It is evident that the hypoxic tumor microenvironment increases the expression of ICAM1.
- ICAM1 increases macrophage migration levels when co-cultured with and without tumor cell condition media. The tumor microenvironment increases migration levels of macrophages.
- ICAM-1 deficient mice with GBM survive longer than wild type mice with ICAM1 and smaller overall tumor volume. ICAM-1 deficient tumors have increased macrophage infiltration and lower expression of ICAM1, have more M1 pro-inflammatory and less M2 pro-tumorigenic macrophages allowing for the mouse to survive longer.
- The expression of ICAM1 in TAMs in hypoxic TME promotes GBM cell invasiveness and migration.

Future Directions

- Determine sex-specific molecular differences between males and females.
- Determine the effects of ICAM1 deficiency and hypoxia or ICAM1 deficiency and radiation on tumor microenvironment and overall survival of mice.
- Determine the effects of ICAM1 deficiency in microenvironment as well as ICAM1 deficiency in glioma cells (CRIPSER construct) on tumorigenesis and survival of mice.

References