UNIVERSITY of WASHINGTON TACOMA

Men are more predisposed to getting Glioblastoma multiforme (GBM) tumor and increased mortality due to genetic predispositions and different molecular pathways

Lisa Fry, Dr. Jutta Heller

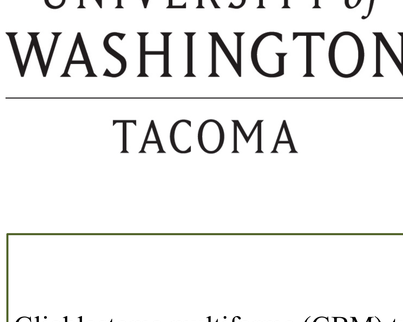
Abstract

Glioblastoma multiforme (GBM) tumor is a highly malignant and cancerous type of brain tumor. It is considered one of the most aggressive and lethal forms of brain cancer. This research paper identifies molecular pathways and genetic mutations contributing to the development of GBM and how they affect men more than women. Data from published research studies has consistently demonstrated that GBMs have an incidence rate 1.6 times higher in men than in women. The research studies used in vivo and in vitro models, functional assays, genomic and epigenomic profiling, cell culture, and clinical trials. Genomic data was collected using genome-wide association studies (GWAS). Findings explicitly show that tumor suppressor genes such as retinoblastoma susceptibility gene (RB1) and p53 (which regulates cell-cycle progression) are inactivated, leading to infiltration of tumor cells. Mutations in epidermal growth factor receptor (EGFR) in the male-only group of one study led to the overexpression of the gene and resulted in uncontrolled growth of tumor cells. Glycolytic gene overexpression and critical mutations in the Isocitrate Dehydrogenase 1 and 2 (IDH1/2) genes have been linked to decreased survival in men. Interestingly, women with overexpressed glycolytic genes and IDH1 mutations survived longer than men with the same type of mutation or a wild-type version and overexpression of glycolytic genes. These findings offer valuable progress towards the understanding and potential treatment of GBM. By understanding the genetic and molecular underpinnings of GBM, researchers can improve prognosis and focus on developing more targeted and effective treatment options.

DESCRIPTION

- Overexpression of genes involved in glycolysis
- P53 and IDH1 mutations more common in men
- Primary gonadal steroid hormone in males linked to GBM growth. DHT(dihydrotestosterone) derived from testosterone was proven to accelerate tumor growth using androgen receptors
- Biological differences identified MGMT (O-6-methylguanine-DNA methyltransferase) promoter methylation as a survival predictor

Figure 1.



(A) Glycolytic pathway demonstrating 11 transcripts (red) whose overexpression confer decreased overall survival within a given sex. **(B)** Overall survival and **(C)** disease-free survival analyses reveal male-specific stratification based upon expression of 11 glycolytic transcripts. Any sample with overexpression of at least 1 glycolytic transcript was placed in the high-glycolytic group. All other samples in that sex were placed in the low-glycolytic group. *P* values were calculated using the log-rank test. Numbers in parentheses refer to number of deaths/total patients in that group (Ippolito et al. 2017).

Figure 2.

Sex-related features of GBM.

Features	Males	Females
Pivotal molecular pathways associated with inherited risk	EGFR	TERT
MGMT hypermethylation	Less frequent	More frequent
IDH1 mutation	More frequent	Less frequent
Cellular pathways potentially predictive of drug response	Cell cycle signaling	Integrin signaling
Clinical response to first-line treatment (Stupp protocol)	Worse	Better

Figure 2. A brief synopsis of sex-related molecular, cellular, and clinical features associated with known or potential clinical relevance in GBM (Matteoni et al. 2020).

Figure 3.

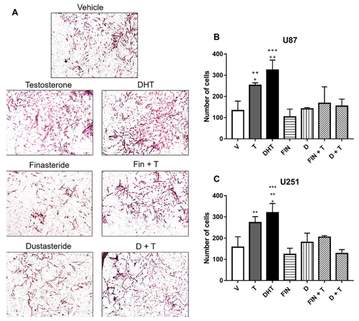


Figure 3. Effect of DHT on GBM cell invasion. **(A)** Representative photographs are observed in an invasion assay at 24 hours with different treatments in U87 cells. **(B)** Graphs of U87, and **(C)** U251 cells represent number of invading cells t at 24 hours with vehicle, testosterone, DHT, Finasteride, FIN+ T, Dutasteride, D + T (Rodriguez-Lozano et al. 2020).

Figure 4.

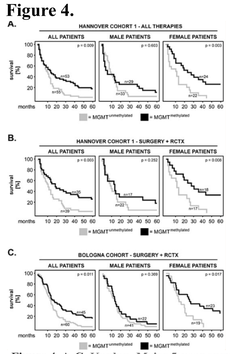


Figure 4. A-C. Kaplan–Meier 5-year survival curves were plotted for the Hannover Cohort 1 patients with methylated versus unmethylated MGMT promoter. Certain gene promoters responsible for controlling growth get turned down, essentially provides a favorable environment for rapid tumor growth (Chen et al. 2016).

SYNTHESIS

- Studies have linked X-chromosome inactivation to tumor suppressor gene RB1 by directly inactivating it.
- As a result, tumor cells grow and multiply without a proper defense mechanism.
- Males are affected by this because they have only one copy of the X-chromosome, which means inactivation can cause a complete loss of function of the RB1 gene located on the X-chromosome.
- Although women undergo X-chromosome inactivation as well, they have two copies of the X-chromosome, therefore RB1 will not be inactivated. Women would have to experience two destructive mutations which is unlikely, while men would only require one.
- RB1 gene is often targeted by HPV strains 16,18,31 and 33. These strains lead to astrocyte cell transformation which is the beginning of GBM development. Most tumors related to HPV in men are due to strain 16. Women are at an increased risk of cell transformation should they have all four HPV strains.
- Gender-based disparities in GBM incidence linked to heritable risk variants in EGFR for males and abnormalities in TERT (telomerase reverse transcriptase) gene for females.
- Males with unmethylated MGMT promoters and elevated FZD7 (frizzled-7) levels have worse prognoses in GBM survival rates
- P53 mutations exhibit sex-specific disparities, influencing GBM susceptibility more in men
- Gain-of-function mutations in p53 impact astrocyte cell transformation and tumor growth, more evident in males than females
- Interactions between p53 mutations and cellular components, such as AP-2gamma (transcription factor) and androgen receptor, contribute to gender-based differences in GBM susceptibility.
- Glycolytic gene overexpression affects GBM survival differently in males and females, particularly impacting men with reduced survival rates
- Hormones like testosterone and estradiol influence GBM growth, with higher levels of testosterone associated with GBM growth in males

Figure 5.

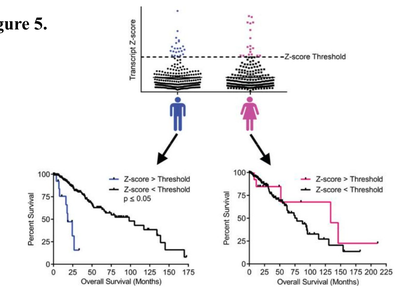


Figure 5. RNA-Seq data from lower-grade gliomas were interrogated for males or females whose overexpression of a specific glycolytic transcript beyond a specific Z-score threshold conferred significantly different ($P < 0.05$) overall survival compared with other individuals within that sex. Significance calculated using the log-rank test (Bao et al. 2017).

FUTURE DIRECTION

- Combining therapies like surgical excision, chemotherapy like Temozolomide (TMZ), and Bevacizumab (immunotherapy) show promise, with better responses seen in female patients.
- Combination therapy involving SGT-53 (tumor targeted nanomedicine) and TMZ to target p53 gene displays potential to delay resistance development, enhancing survival in GBM
- Anti-angiogenesis treatment normalizes GBM microvasculature, inhibits vessel growth, reducing tumor vascularization and infiltration, possibly limiting fluid leakage and improving treatment effectiveness.
- Tailored therapies based on genetic subtypes in GBM and ongoing clinical studies targeting specific subtypes show promise, potentially advancing immune-based personalized therapies.
- Understanding sex hormones' impact on GBM is crucial, necessitating models to explore hormone differences.

Figure 6.

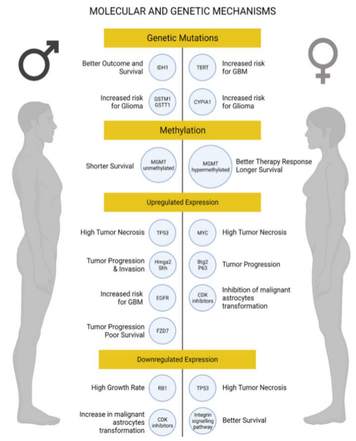


Figure 6. Summary of genetic and molecular mechanisms associated with glioblastoma in men and women (Wu et al. 2021).

REFERENCES