

## Review article

**Sex hormone receptors and glioblastoma**Ashwini K.<sup>1</sup>, Shilpa S. Shetty<sup>1</sup>, Ananthan Raghotham<sup>2</sup>, Suchetha Kumari N.<sup>1</sup>, Praveen Kumar Shetty<sup>1</sup><sup>1</sup>Department of Biochemistry, <sup>2</sup>Department of Neurosurgery, KS Hegde Medical Academy, Nitte (Deemed to be University), Mangalore, Karnataka, India

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Corresponding author: **Suchetha Kumari N.** Email: kumarin@nitte.edu.in**ABSTRACT**

Glioblastoma (GBM) is the primary brain tumor of the central nervous system which is most common and the most aggressive of all other types of tumors. Current therapy for GBM involves surgical removal (excision) of the tumor followed by radiotherapy with concomitant and adjuvant therapy with temozolomide. Despite the improvement in therapy for GBM, survival of the patients remains poor, only up to 1 year. Treatment for GBM is limited due to the presence of blood brain barrier which prevents the entry of molecules with molecular weight >500 Dalton. Various gene mutations or over expressions lead to GBM growth. Evidence from the earlier reports suggest that epidermal growth factor receptor is overexpressed in 60% of GBM. Interestingly, recent studies have suggested the involvement of sex hormones in the development and progression of GBM though the underlying mechanism of action of these hormones is poorly understood. In this review, we discuss the role of sex hormones and their receptors, a contributing factor in the development of GBM.

**Keywords:** Glioma; glioblastoma; sex hormone receptor; blood brain barrier.

**INTRODUCTION**

**C**ancer is a major cause for death worldwide. Globally cancer risk would increase by 60% over the next two decades (1). Cancer results due to abnormalities arising in the genome of cells during the cell division, altering the genetic expressions of proteins that are mainly involved in targeting tumor suppressor proteins, growth factors, and transcription factors. These genetic alterations lead to the transformation of normal cells into malignant cancer cells that do not undergo apoptosis, avoid detection by the immune system and multiply rapidly (2,3). Glioblastoma multiforme (GBM) is the most common primary malignant neoplasm of the central nervous system in adults. Glioma is a type of brain tumor that arises from abnormalities in glial cells. Main function of glial cells is supplementation of nutrients to the neurons and to maintain the blood brain barrier (BBB). Glioma is a term used in describing the different types of glial tumors which include astrocytoma, oligodendroglioma, ependymoma, mixed glioma and so on (4). Sex hormones include androgens, estrogens, progesterone, and prolactin hormones not only involved in reproductive functions but also play a role in pathological conditions including tumor growth and survival. Their role in prostate cancer, breast cancer, ovarian cancer is well established but mechanism action in GBM remains poorly understood and controversial. Sex hormonal receptors are expressed in the brain involved in neuronal protection and various other functions. Hence, we take up this review to explore the importance of sex hormonal receptors and their importance as contributing factor in GBM by compiling some of already published data and

emphasizes the use of various receptor agonists and antagonists as a therapeutic modality in GBM.

**Classification of glioma**

One of the major types of gliomas is astrocytoma. Astrocytes are the star shaped cells most abundantly present in central nervous system (CNS) and perform functions in axon guidance and synaptic support to control the blood brain barrier and the blood flow (5). Glioma accounts approximately 30% all brain and CNS tumors and 80% of malignant tumor. Astrocytoma is graded in a scale of I to IV based on severity. GBM is classified as WHO (World Health Organization) Grade IV Astrocytoma, the highest grade, and the most malignant type (6). Glioblastoma is the most common malignant brain tumor occurring adults of age 45-65 and is the most lethal of all cancers. The histologic features that distinguish glioblastoma from all other grades are the presence of necrosis (dead cells), microvascular proliferation and increase of abnormal growth of blood vessels around the tumour (7). Molecular profiling by Cancer Genome atlas (TCGA) has further classified GBM as- Classic, Mesenchymal, Neural and Proneural based on aberrantly expressed genes.

**Risk factors associated with glioma**

There are no conclusive data available on the risk factor contributing towards GBM. Glioblastomas alone accounts for 60-70% of all gliomas, anaplastic astrocytoma 10-15%, anaplastic oligodendrogliomas and anaplastic oligoastrocytomas 10% and the remaining 5-20% belong to less common tumor types, such as anaplastic ependymomas and anaplastic

gangliogliomas (8). Exposure to ionizing radiation can increase the risk of developing GBM. Other factors including smoking, diet, usage of cell phones, severe head wounds, occupational risk, exposure to pesticides shown to have no association towards GBM development (9,10).

### **Glioblastoma diagnosis and treatment**

Although there has been an improvement in GBM diagnosis and treatment, patient survival rate remains poor, only around 15-23 months. Despite of therapeutic modalities in GBM, there is recurrence due to molecular heterogeneity of GBM tumors and poor penetration of therapeutic drugs through the blood brain barrier. Both these factors affect the treatment response and prognosis there by leading to acquired tumor resistance in GBM patients (11). Treatment outcomes even after multimodal therapies, including surgical resection, radiotherapy, and chemotherapy, remain poor; the median survival is only up-to 1 year (7,8). The treatment of GBM is limited due to the presence of BBB which prevents the entry of molecules with >500Da molecular weight (12). Current therapy for GBM involves surgical removal (excision) of the tumor followed by radiotherapy with concomitant and adjuvant therapy with temozolomide (TMZ) (7,8). If there is further progression, Bevacizumab is widely used alone or in combination with Lomustine which acts against the circulating Vascular Endothelial Growth Factor (VEGF). Despite of large number of clinical trials, the identification of candidate therapeutic strategy to treat GBM is complex due to various factors including disease heterogeneity. Therapeutic modality should take account of size and location of the tumor, previous treatments, age, Karnofsky Performance Score (KPS), patterns of relapse and prognostic factors.

### **Current diagnostic and therapeutic challenges**

As explained above current therapy for GBM includes maximum resection of the tumours combined with radiation therapy and concomitant adjuvant therapy with TMZ. Mechanism action and target of Food and Drug Administration (FDA) approved drugs for GBM are not fully understood. Out of six drugs that are approved for GBM treatment, three acts as DNA alkylators, two are kinase inhibitors and one is tubulin inhibitor. BBB inhibits the delivery of large number of drugs, including antibiotics, antineoplastic compounds and other molecules to pass through endothelial capillaries to brain. Main challenge in developing novel drug to treat GBM is difficulty in reaching concentration at the target site. Only few methods exist for permeation of the membrane for drugs, however new drug delivery systems are developed using high throughput screening receptor-ligand interaction which helps in identification of appropriate drug among many

compounds. Drug should not only be selected based on high binding affinity to receptor in high throughput screening, but should be suitable on the basis of structure-activity relationship, target receptor binding and behaviour in animal model system. Molecules like glucose and lipid soluble drugs can easily cross BBB. Similar to BBB, brain tumour micro vessels/capillaries also limit drug delivery to brain. This can cause failure in drug deliver to brain and difficulty in treating brain tumours. Thus a molecule with smaller molecular weight, more lipophilic nature and lesser neurotoxicity should be developed in treating GBM.

### **Biomarkers of GBM**

Some molecular markers are still under investigation, but few of them have been already tested in GBM which includes O<sup>6</sup>-methylguanine DNA methyl transferase (MGMT), Isocitrate Dehydrogenase (IDH), Epidermal Growth Factor Receptor (EGFR), Vascular Endothelial Growth Factor (VEGF), Tumor Suppressor Protein TP53, Phosphatase and Tensin Homolog (PTEN), p16INK4a gene, Phospholipid metabolites, cancer stem cells and recently also imaging biomarkers (16). A most common mediator of GBM progression is EGFR which is amplified in 40%, is also found to be mutated, amplified, or over expressed in GBM. p53 is generally a tumor suppressor protein which play role in formation of high-grade tumors. PTEN is mutated 5-40% in GBM. IDH involved in tricarboxylic acid cycle (TCA) that catalyzes the formation of  $\alpha$ -ketoglutarate. If this enzyme is mutated it produces D-2 Hydroxyglutarate whose accumulation is harmful and induces epigenetic modification leading to aberrant gene expression (13). Patients with GBM show better response to chemotherapy with Temozolomide. IDH mutation correlates with MGMT methylation that is most of the patients with IDH mutation also have MGMT promoter methylated. But also, without IDH mutation only MGMT methylation also observed in 40% GBM cases. Several studies have shown that apart from these markers, there is also change in the expression of Androgen Receptor (AR), Estrogen Receptor (ER), Progesterone Receptor (PR) and Prolactin Receptor (PRLR) in GBM. Their role in breast cancer, prostate cancer is clearly understood, but their involvement in GBM is poorly understood.

### **Sex hormones**

Sex hormones include estrogen, progesterone and testosterone that regulate variety of cellular functions not only in the reproductive tissues but also in non-reproductive tissues (14). Synthesis of androgen and its precursor dehydroepiandrosterone (DHEA) in females occur in adrenal glands and ovaries. Estrogens synthesized in ovary, placenta, testes, and adrenal cortex, contribute to the development of female sexual characteristics, and enhance

endometrial growth (15). Progesterone is produced in ovaries, adrenal glands, and placenta, and is involved in the regulation of reproductive functions which include menstrual cycle and maintenance of pregnancy. Prolactin (PRL) is the peptide hormone which is synthesized and secreted from specialized

cells of anterior pituitary gland (16). It is principally involved in the regulation of lactation and fertility. All these sex hormones are synthesized and circulated in the brain cells and they function through interacting with their respective receptors.

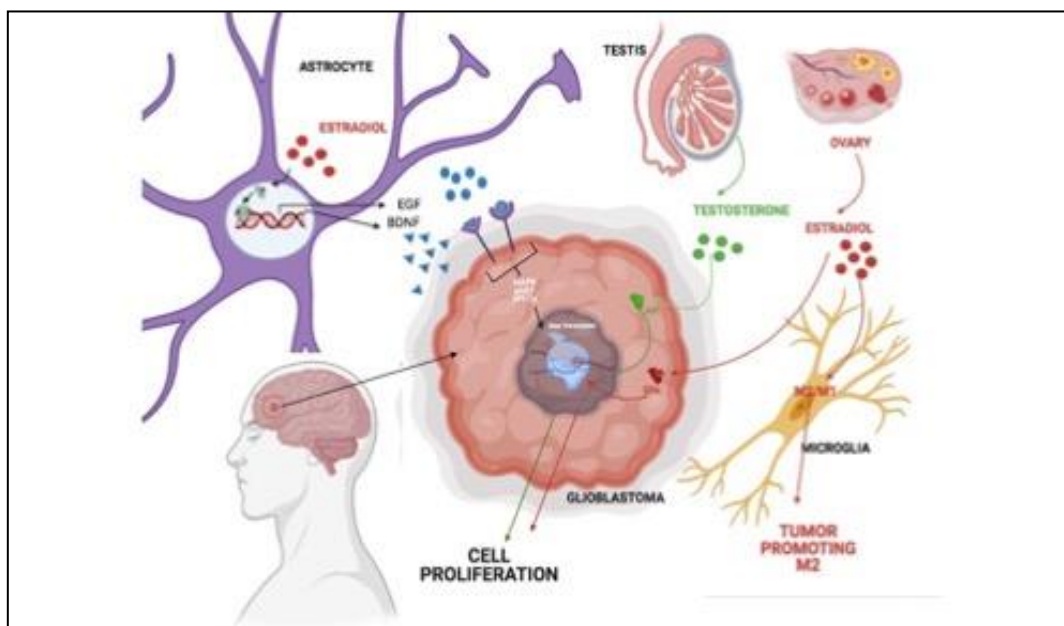


Fig.1: Summary on the role of sex- hormones in glioblastoma (created using Biorender.com)

### Sex hormones their receptors and brain functions

Animal studies have provided the evidence that sex hormones bind to their respective receptor and mediate various genomic effects through activation of various signaling pathways. Sex hormonal receptors have been found in brain regions, including hippocampus and claustrum for estrogens and amygdala, cerebellum, hippocampus, and hypothalamus for progesterone (17). Receptors of sex hormones such as Estradiol (ER $\alpha$  and ER $\beta$ ), Progesterone (PR A and PR B), Testosterone (AR) are highly expressed in hypothalamus and limbic system (18,19). Higher ER $\alpha$  expression in the hippocampus region contributes towards memory and spatial recognition (20) in rats, including humans. AR neurons are found in the limbic areas such as hypothalamus. Limbic area is involved in the control of endocrine function and expression of sexual behavior. AR mRNA containing cells are observed in forebrain, mid brain, brainstem, and spinal cord (21,22).

### Sex hormone receptors in glioma

Although sex hormones and their receptors are most involved in sexual functions, their expressions are also involved in pathological processes such tumor growth. Their involvement in breast cancer, ovarian cancer, and prostate cancer is well understood but their role in development of aggressive brain tumors such as GBM remains unelucidated.

Some studies suggest the role of female sex hormones

in GBM progression. Several studies have shown the presence of Progesterone (P) in GBM, PR B is the predominant isoform in the patient derived tumour sample (23). It is also reported that the involvement of P in enhancing or reducing the expression of various genes involved in proliferation, metabolism and various immunological processes involved in the development and progression of GBM. Mechanism of malignant tumors escaping from the immune control includes the expression or secretion of immune modulatory molecules leading to the uncontrolled growth, neo-angiogenesis, and invasion into adjacent tissues. One of such agents is Progesterone Induced Blocking Factor (PIBF), which is a protein with molecular weight of 34kDa secreted by  $\gamma/\delta$  T lymphocytes. PIBF participates in regulation of cell cycle (24). PIBF expression was found in proliferating cells such as human trophoblasts, mesenchymal stem cells and in malignant tumors. PIBF expression was also found in both cytoplasm and nucleus of patient derived tumor sample (25). Clinical trials using mifepristone, a PR antagonist showed that it could cross BBB could be considered in therapy for patients with chemotherapy-resistant brain cancer (26). Higher concentration of estrogen found in the GBM biopsies compared to low grade astrocytoma. Two of the estrogen receptors ER  $\alpha$  and ER  $\beta$  functions differently in GBM. ER  $\alpha$ -36, a variant of estrogen receptor alpha 66 (ER $\alpha$ -66) can mediate cell proliferation by estrogen or anti estrogen signaling in different cancer cells. ER  $\alpha$ -36 expression was higher in GBM cells (27). AR, ER $\alpha$  and their co activators SRC-1 and SRC-3 expression was observed

in patient derived tumor samples (28). Androgens along with its receptors, AR regulates various gene expressions and involved in tumor growth. AR expression in GBM was higher than the normal brain tissue (29). These are the few evidences showing involvement of sex hormones and their receptors in glioma.

### Progesterone receptor in glioma

Progesterone promotes growth, migration and invasion of human astrocytoma cell lines which includes U372 (Grade III), U87 and D54 (Grade IV or GBM). In these cell lines effect of P4 is mediated by progesterone receptors and treatment with receptor antagonists like Mifepristone almost completely block the action of this hormone. One of the known target gene of PR is PIBF which was initially discovered in the maternal lymphocytes. PIBF found to be associated with development of cancer. Several reports have shown that over expression of PIBF was found in biopsies of uterus, breast, stomach and in brain (25,30). Progesterone induces both *in vitro* and *in vivo* proliferation and invasion of GBM mediated through activation of PR. There is also report suggesting that isoform of PIBF act as ligand in the activation of JAK1/STAT6 pathways. Activation of JAK2/STAT3 known to promote cell migration and invasion in several types of cancers and is also overexpressed in GBM. A study also demonstrated that PIBF bind to promoter region of IL-6, which is over expressed in GBM which act as ligand for JAK2/STAT3 pathway. Thus, this might be one of the underlying mechanisms effecting the cell migration in glioblastoma.

### Estrogen receptor in glioma

ER  $\alpha$ -36, a splice variant of ER  $\alpha$  identified as novel mediator of breast tumorigenesis. Different researchers have reported the expression of ER- $\alpha$ 36 in human breast cancer, human bone tissue, glioma cells, hippocampus, and neuron-like PC12 cells. Li *et al.*, found that ER- $\alpha$ 36 (27) is involved in development of acquired TAM resistance by regulating the growth status switch in breast cancer cells. It activates ERK 1/2 through Protein Kinase-C delta signaling pathway which leads to expression of cyclin D1/CDK4, thus increasing cell progression. In addition, binding of ER  $\alpha$ -36 to ERK prevents its dephosphorylation by MKP-3 and enhance Paxillin/Cyclin D1 pathway. In this study ER- $\alpha$ 36 expression was higher in GBM cells and involved in the tamoxifen (TAM) sensitivity in GBM cells (27). *In vitro* studies showed that ER $\beta$  agonists increase the sensitivity in GBM cells to therapeutic agents such as Temozolomide and Lomustine. But the mechanism behind this is poorly understood. ER $\beta$  sensitizes GBM cells to carboplatin, cis platin, lomustine and temozolomide treatment. Using xenograft models the study provided the evidence that tumor suppressor potential of ER $\beta$  and ER $\beta$  sensitizes

GBM to Temozolomide treatment (31).

Reduced expression of ER $\beta$  was found in higher grade tumor tissue. ER $\beta$ 5 was the main ER $\beta$  isoform which was found in gliomas (33). Hypoxia induced ER $\beta$ 5 expression in glioma as a self-protective mechanism against tumor proliferation and might be an important therapeutic target in treating glioma. Use of selective ER $\beta$  agonists like DPN, MF101 and liquiritigenin has the capability to inhibit glioma cell proliferation and tumor growth (31).

### Androgen receptor and GBM

It has been notably found that expression of AR was higher in the biopsies of GBM patients in comparison with the normal (29). Interaction with Androgen receptors, Testosterone induces proliferation, migration, and invasion in human GBM cells (33). There is also a report on the response to physiologically concentration of metabolically stable androgen (R1881), the small VCP/p97 interacting protein (SVIP) expression is down regulated by AR in prostate cancer cell line LNCaP. SVIP function as endogenous inhibitor of endoplasmic reticulum associated degradation (ERAD). SVIP also induce localization of VCP/p97 to plasma and lysosomal membrane and regulate autophagy. A tumor suppressor protein, p53, is found to be inactivated in most of the cancers, leading to inhibition of apoptosis. Expression of AR increased as the tumor grade progressed (29). Studies have shown the amplification and overexpression of AR in GBM (34). The variant AR-V7/AR3 lacking LBD, mediate ligand independent AR activation in prostate cancer. Presence of such variant in GBM, along with the finding that silencing of full-length AR induce GBM cell death might be a role played by AR in GBM growth. This was the first study to show that AR is amplified at DNA, RNA, and protein level in GBM samples of both men and women. The study also showed that use of AR antagonist such as Enzalutamide, efficiently reduce the growth of GBM (35).

### CONCLUSION

Glioblastoma (WHO Grade IV) is rapidly growing, destructive tumor which leads to death within a few months. Even after the improvement in therapy survival of the patient is poor, this might be due to the molecular heterogeneity in GBM. Sex hormones are secreted throughout one's life involved in various functions of the body. There is a change in their expression pattern in the various stages of life in both men and women. They are also expressed in CNS where most importantly function in protecting the neurons. Change in the hormone level can be both useful and it may be harmful which may lead to tumor growth. Recently published reports suggested that sex hormone receptors are also involved in the progression of glioblastoma. These studies report that

sex hormones mainly interact with their receptors and act as a contributing factor in GBM. Few studies have already utilized available receptor antagonists which showed very good results in patient derived tumor cells, cell lines and animal model. These antagonists, (some of which are already in clinical trial) should enter clinical trial to check their therapeutic potency in treating GBM. Blood brain barrier is one of the major obstacles which prevents entry of larger molecules into the brain. Hence a small molecule, with lesser neurotoxicity should be developed in treating GBM or any other brain related diseases. Thus, sex hormones not only are involved in reproductive functions, they also can cause pathological conditions such as tumor growth. Therefore, these sex hormone receptors which are expressed in brain are the potential therapeutic targets and should gain more and more attention in the development of a variety of drugs in GBM prevention and treatment.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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