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Emerging Significance of Estrogen Receptor β in Gliomas

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Primary brain tumors are heterogeneous group of intracranial lesions that are categorized into different subtypes based on their close morphology to their parental cell. Gliomas are the most common and deadliest tumors that accounts for ~70-80% of total brain tumors and the etiology of brain tumors is not completely understood [1-3]. Recent evidence suggests that the incidence of brain tumors is significantly higher in men than in women during the periods of active menstrual cycle suggesting the possible protective role of female sex hormones in the development of brain tumors [4-6]. Furthermore, a lower glioma incidence was reported for females who used exogenous hormones. The existence of a gender bias and the involvement of steroid hormones in the development of gliomas highlight the importance of this field in the glioma pathobiology.

Estrogens are the steroid hormones that play a crucial role during development and differentiation of central nervous system [7,8], and locally synthesized estrogens play an essential role in neuroprotective functions [9]. The biological effects of estrogens are mediated through their cognate receptors: estrogen receptor alpha [ERα] and estrogen receptor beta [ERβ] [10]. ERβ has quite a different function than ERα and ERβ functions as a tissue-specific tumour suppressor with anti-proliferative actions [10,11]. Several studies demonstrated that most of the gliomas express ERβ with negative or weak expression of ERα. ERβ is highly expressed in low-grade astrocytomas and non-neoplastic brain tissues. In contrast, most of the high-grade tumors express low ERβ expression and this lower ERβ expression correlates with histological malignancy and poor survival of patients [12-14]. Lower ERβ expression is significantly associated with higher expression of cytoplasmic BAG-1 [a coregulator of ER signalling] and worse clinical outcome [14]. Further, high expression of ERβ was an independent favourable prognostic factor [15].

ERβ is expressed in five different isoforms as a result of alternate splicing and promoter usage [11]. Each ERβ isoform has a unique function, and isoforms have the potential to modulate wild-type ERβ [ERβ1] transcriptional activity through hetero-dimerization [10,16]. A recent study showed that ERβ1 and 5 are the major ERβ isoforms expressed in human gliomas [17]. ERβ ligands have the potential to up regulate expression of the ERβ [13]. Hypoxic conditions increase the expression of ERβ isoforms in glioma cells and overexpression of ERβ1 and 5 increases PTEN expression, leading to negative regulation on the PI3K/Akt/mTOR and MAPK signalling, supporting the tumour suppressive functions of ERβ in gliomas [17].

Even though estrogen signals through ERβ, estrogen as a potential therapy to gliomas has limited therapeutic application due to safety concerns including uterine cancer, heart disease, and feminization in men. Although ERα and ERβ are structurally similar, they have differences in ligand binding domains that differ enough to be selective in ERβ isoform–specific ligand binding. In addition ERα and ERβ have different cellular expression and function and regulates unique sets of downstream target genes [11] by binding to different sites on DNA and by the recruiting different co-regulatory and chromatin remodelling proteins [18]. The unique ERβ ligand binding domain and ERβ-specific gene activation functions suggest that the use of selective ERβ modulators will have immediate clinical utility in treatment of gliomas.

Recent studies identified liquiritigenin [LIQ] isolated from the plant Glycyrrhiza uralensis [19] and S-equol isolated from soy isoflavone daidzein via biotransformation as ERβ-specific agonists [20]. Several ERβ selective drugs are being investigated as replacements for estrogen to treat menopause symptoms including DPN, ERB-041, MF101, S-equol, and LIQ [10]. In Phase II and III clinical trials, LIQ and S-equol were found to be safe, well tolerated and taken with high compliance. Further, ERβ agonists have good blood–brain barrier permeability and less neuronal toxicity [21,22]; hence, they are very suitable for therapeutic treatment of gliomas. Recent studies using in vitro and in vivo preclinical models also demonstrated that ERβ agonists have the potential to inhibit glioma cell proliferation, and mechanistic studies showed ERβ agonists reduce the growth by decreasing the proliferation of tumour cells and by inducing apoptosis [13].

In summary, evolving findings suggest that ERβ functions as a tumor suppressor in gliomas with anti-proliferative actions. Although the potential importance of ERβ as a therapeutic target has been appreciated, the clinical utility of ERβ agonists is limited because of the lack of mechanistic insights, the lack of understanding of the role of ERβ isoforms and the altered expression/localization of ERβ in advanced glial tumors. Because, estrogens play a critical role in the differentiation and survival of neural cells, discovery of ERβ-specific agonists open new avenues for the development of novel therapeutics acting through ERβ to prolong survival in patients with gliomas. Future studies examining the molecular mechanism of ERβ signaling and the functions of ERβ isoforms in glioma progression will be useful in maximizing treatment opportunities for this deadliest cancer.

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