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The language of glioblastoma: A tale of cytokines and sex hormones communication

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Abstract

Glioblastoma (GB) is the most aggressive and frequent tumor in the central nervous system and, in humans, represents the worst prognosis for cancer. GB develops a very complex microenvironment, recruiting and interacting with a variety of cells and soluble factors, including immune cells, cytokines, and sex hormones, that contribute to GB survival and progression. Recent evidence has shown a crosstalk between cytokine and sex hormone signaling in GB. This communication could provide GB resistance to treatments and malignancy. Then, how GB orchestrates this communication is a matter of interest. For instance, a critical interaction between tumor necrosis factor-beta (TGF-β) and estrogen receptor signaling has been reported in regulating epithelial-mesenchymal transition, an essential step in GB progression. Furthermore, an inhibition of TGF-β signaling by androgen receptor has been reported to promote GB tumorigenesis in men. Conversely, it has been described that cytokines regulate steroid hormone production in different organs, and this mechanism could be involved in GB development and progression. All these data suggest an intercommunication between the immune and endocrine systems in the tumor microenvironment. Thus, in this review, we focus on explaining the knowledge about this critical intercommunication system and its implication in GB progression.

Key Points

- Sex hormones can regulate GB cell proliferation, migration, and invasion.
- Cytokines in the GB microenvironment are fundamental in tumor immunosurveillance evasion.
- Intercommunication between sex hormones and cytokines in the GB microenvironment is critical to tumor progression.

The immune system is commonly perceived as an isolated entity, with the principal function being the elimination of pathogen microorganisms, maintaining body homeostasis. However, recent evidence has shown that the immune system interacts in a complex and elegant web of communication with the endocrine system; this interaction is crucial to coordinating the organism's responses to environmental stimuli.[1,2] Although these systems are physiologically separated, they can interact through a tight communication network that involves hormones and cytokines.[3] Then, hormones can influence the immune system, and cytokines can affect the endocrine system as a product of immune system activation.[4] Therefore, dysregulation of loss of the integrity of these systems could be a factor in developing some diseases like cancer.[5]

Glioblastoma (GB) is the most frequent and aggressive cancer in the brain, and recently, it has been shown that the tumoral microenvironment (TM) is characterized by abundant immune cell infiltration, which appears to reduce the immune response against the tumor.[6] Then, GB can communicate with immune cells to promote tumor stabilization and progression in the brain.[7] GB can secrete a variety of cytokines, including interleukin-6 (IL-6), interleukin 1-beta (IL-1β), tumor necrosis

factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), which promote GB immune evasion and progression.[8] In TM, GB can be infiltrated by a great diversity of immune cells, including microglia, monocytes, macrophages, neutrophils, NK cells, and lymphocytes.[9,10] Additionally, it is well recognized that, in TM, GB hormones play an essential role in tumor growth. Furthermore, recent investigations have started to elucidate the interaction between hormones and the regulation of TM in GB development, strongly suggesting the role of steroid hormones.[11,12] It has been shown that both female sexual hormones, estradiol (E2) and progesterone (P4), and testosterone (T) influence GB cell progression, migration, and invasion. Additionally, reports have demonstrated that in GB patients, there exists an increment in testosterone levels and high expression of the androgen receptor (AR). These data are related to the fact that GB is more frequent in men than women.[13–15] However, the influence of hormones on the TM immune component in GB has not been fully explored. In normal brain tissue, the principal innate immune cells are microglia, and it has been reported that in mice, sex hormones modify the morphology and quantity of microglial cells.[16] Recently, it has been described that changes in sex hormone concentration and their receptors are fundamental in regulating immune cell functions.[17] Generally, androgens are considered immunosuppressive stimuli; they can influence antibody production, T cell proliferation, NK cell cytotoxicity, and the production of anti-inflammatory cytokines.[18] While estrogens and progestins present a dual role, in low concentration, they are considered immunoreactive stimuli, increasing pro-inflammatory cytokines production, whereas, in high concentrations, as in pregnancy, they induce a tolerogenic state, diminishing specific immune functions.[19] However, TM of GB context is a field that requires more attention to elucidate how sex hormones impact immune responses and, thus, tumor progression.

Main Cytokines in Glioblastoma Tumor Microenvironment

Cytokines are responsible not only for immune system control but can regulate hematopoiesis and embryo development. It has been described that cytokines can be secreted by the central nervous system (CNS) cells, such as neurons, astrocytes, and microglia cells, thus requiring a delicate regulation of their production and secretion to maintain homeostasis.[20–23] When cytokines are recognized by their specific receptors, they activate distinct signals that regulate specific cellular responses, including cell migration, differentiation, and activation of gene expression.[24] In the CNS, cytokines regulate immunological, neuroendocrine, and neurochemical systems.[25] It has been described that cytokines play a dual role in tumor progression and treatment depending on the type of tumor.[26] It is well described that tumors that do not produce or produce very low amounts of pro-inflammatory cytokines or produce large amounts of anti-inflammatory cytokines limit tumor growth. In sharp contrast, overproduction of pro-inflammatory cytokines can regulate angiogenesis and promote tumor growth.[27] Therefore, several evidences show that cytokines do not exclusively operate; they function depending on the context.[28] Then, in this review, we describe the expression and the effects of cytokines in the TM of GB.

Interleukin-6 (IL-6)

IL-6 is produced by different cell types, including T cells, B cells, monocytes, neutrophils, endothelial cells, and fibroblasts, and in the CNS, it has been reported that neurons and glial cells produce IL-6.[29,30] IL-6 is involved in different functions, such as increasing endothelial permeability, leukocyte recruitment, and infiltration to sites of inflammation, promoting leukocyte maturation, and regulating the acute phase of inflammation.[31,32] IL-6 interacts with its receptor (IL-6R) at the cell membrane, recruiting the glycoprotein 130 (gp130), and activating a classical signal transduction IL-6 pathway.[33] However, it is essential to note that while gp130 is expressed in all nucleated cells, IL-6R is expressed in leukocytes and hepatocytes. Furthermore, gp130 alone cannot recognize IL-6. A soluble form of IL-6R (sIL-6R) can recognize IL-6, similar to the membrane IL-6R, and interact with gp130 at the surface of cells that do not express IL-6R, activating a mechanism called trans-signaling of IL-6. Interestingly, some reports show that IL-6 trans-signaling activation induces a pro-inflammatory response while IL-6 classical signaling induces an anti-inflammatory response.[34] Neurons and glial cells also express IL-6R and gp130, so IL-6 can participate in an autocrine way or activate neighboring cells.[30] Additionally, it has been described that IL-6 coordinates neural stem cell (NSC) differentiation to neurons and glial cells. NSC neuron differentiation depends on sIL-6R through activation of MAPK/CREB (mitogen-activated protein kinase/cAMP response element-binding protein) signaling; NSC glial differentiation requires activation of STAT-3.[35] It is well described that IL-6 is fundamental in recruiting neutrophils and monocytes to sites of infection and inflammation. It induces the expression of adhesion molecules on endothelial cells, essential to leukocyte adhesion and extravasation into tissues. Additionally, IL-6 recognition in endothelial cells can activate the production of chemokines like IL-8 and MCP-1, promoting leukocyte recruitment (Figure 1).[36]

In the human GB cell line U87MG, the expression of IL-6 and IL-6R has been reported. Furthermore, the blockage of IL-6-IL-6R inhibits U87MG cell growth. This result suggests a possible autocrine stimulation of IL-6 in GB cell line U87MG.[37] Additionally, in U251 and T98G GB human cell lines, IL-6 induces cell migration and invasion (Figure 1). These tumors have been classified into 3 groups: classical, proneural, and mesenchymal, with different characteristics that could influence their interaction with the tumor microenvironment, resulting in differences in the establishment and tumor progression.[38] It has been described that U251 presents proneural characteristics, whereas T98G and U87MG present mesenchymal characteristics; therefore, cellular behavior among cell lines could present differences.[39,40] In fact, it has been reported that the protein pattern expression differs among GB cell lines.[41] Besides, it has been reported that the variability of GB cell models

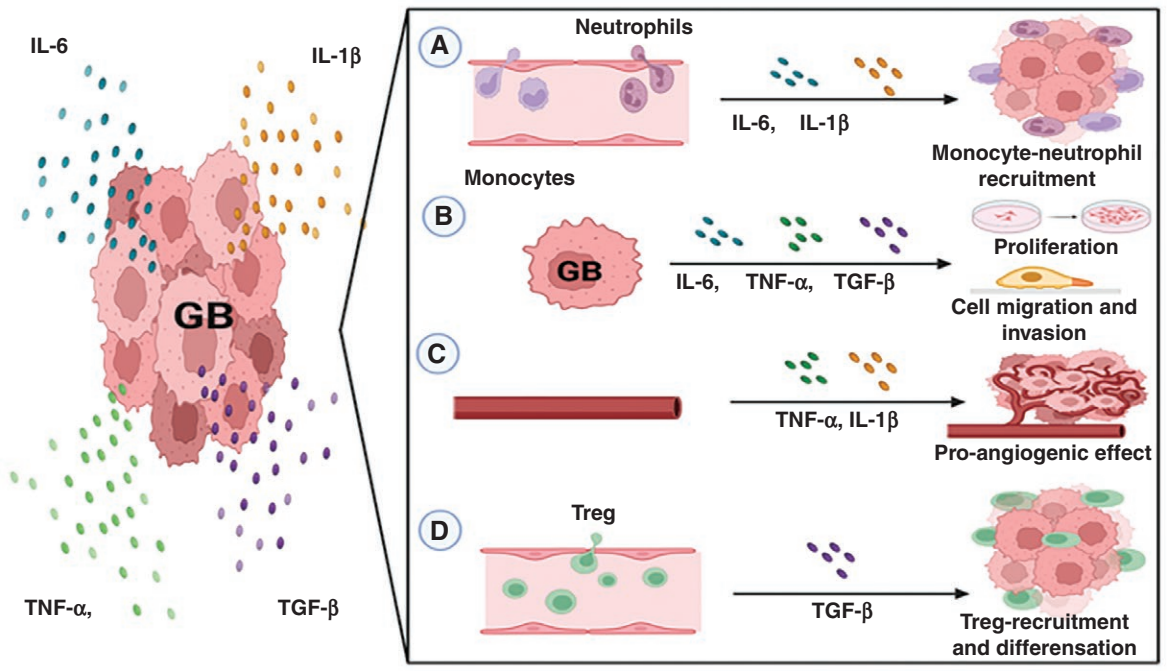

Figure 1. Main Cytokines in GB-Tumor Microenvironment (TM). GB can secrete various cytokines, which help GB immune evasion and tumor progression. Including IL-6, IL-1β, TNF-α, and TGF-β. All induce an autocrine effect in GB cells but activate different responses. (**A**) IL-6 and IL-1β induce monocyte-neutrophil recruitment. (**B**) IL-6, TNF-α, and TGF-β induce GB cell migration, proliferation, and invasion. (**C**) In response to TNF-α or IL-1β produces a proangiogenic effect in TM. D) In the TM, TGF-β Induces Treg recruitment and differentiation, which results in immune suppression.

could be affected by culture conditions showing alterations in genomic and transcriptomic levels.[42] The significant variations in IL-6 responses in GB cell lines suggest differences in the signaling activated by IL-6 in each cell line. It has been shown that in U251, T98G, and U87MG cell lines, IL-6 induces the activation of STAT-3 signaling. Nevertheless, in U251, IL-6 induces ERK1/2 phosphorylation, while in T98G, IL-6 treatment decreases ERK 1/2 phosphorylation in a dose-dependent fashion.[43,44] This observation could explain why the IL-6 effect in GB cell lines could differ depending on the cell line. Thus, more studies are needed to describe IL-6 signaling in GB cell lines. In addition, it has been reported that the expression of IL-6 mRNA is related to the tumor grade. In biopsies of different grades of gliomas, including astrocytoma grades I, II, and III, IL-6 mRNA expression was lower than in GB.[45] Finally, overexpression of IL-6 mRNA correlates with diminished GB patient survival. GB patient biopsies with high levels of IL-6 mRNA showed decreased patient survival.[46] All these results suggest IL-6 overexpression as a biomarker of malignancy and survival in GB patients.

Interleukin 1-Beta (IL-1β)

IL-1β is one of the major cytokines that regulate inflammation, and it is secreted by several cell types, including innate immune cells, and in the CNS by astrocytes and microglia cells.[47,48] IL-1β is produced as a precursor, known as pro-IL-1β. After a stimulus such as an injury or infection, pro-IL-1β is cleavaged by caspase-1 and then secreted to the media.[49] Once IL-1β is secreted to the media, it is sensed by IL-1R in the plasmatic membrane of the glial cells mediating the production and secretion of more inflammatory mediators such as IL-6 and prostaglandin-E(2) (PGE(2)), by activation of nuclear factor-kappa B (NF-κB) and the extracellular signal-regulated protein kinase (ERK1/2) guiding the progression of inflammation in the CNS.[50] Moreover, IL-1β has been shown to play a role in the GB progression. In response to IL-1β, U251 and U87MG GB cell lines secreted more IL-1β and the high IL-1β conditioned media of U87MG promotes angiogenesis and neurotoxicity in human umbilical vein endothelial cells and neurons, respectively.[51] It was reported that IL-1β stimulation increased IL-8 and CCL2 secretion in the U251 GB cell line, suggesting monocyte-neutrophil recruitment and proangiogenic environment (Figure 1).[52] Additionally, a report in a mouse model of GB has shown that monocyte infiltration in TM produces more IL-1β activating IL-1R in GB cells, inducing an interplay between GB and monocytes that promotes tumor progression.[53] These reports suggest a crucial circuit between GB and immune cells via IL-1β. Therefore, IL-1β could be a promising target in GB diagnosis and treatment.

Tumor Necrosis Factor-Alpha (TNF-α)

In the CNS, TNF-α is critical in regulating homeostasis and pathologic states by activating chronic and acute inflammatory responses. TNF-α is produced by different immune

cells, including macrophages, mast cells, granulocytes, T cells, and natural killer (NK) cells. Microglia, astrocytes, and neurons are the main sources of TNF-α in the CNS.[54] For instance, in response to lipopolysaccharide (LPS), microglia cells secreted TNF-α.[55] As mentioned above, TNF-α participates in pathological states and has been implicated in oligodendrocyte proliferation, survival, and nerve remyelination.[56] Additionally, the use of different TNF-α blockers has been involved in demyelination disorders.[57] In U251, U87MG, and patient-derived primary glioma cells, TNF-α increases cell proliferation, and only in U251 cells increase cell invasion, suggesting a differential expression of TNF-α receptors in GB (Figure 1).[58] It was reported that TNF-α operates as a message in the GB-monocytes-endothelium intercommunication to induce tumor vascularization. First, U251 secretes IL-8 and CCL2; this induces TNF-α monocyte secretion, and finally, TNF-α induces endothelial cells VCAM-1, ICAM-1, CXCL5, and CXCL10 expression typical proangiogenic molecules (Figure 1).[59] Then, due to the heterogeneity response to TNF-α in the GB context, it is critical to continue studying the role of TNF-α in the context of TM in GB to understand the TNF-α effects and, in the future, propose as a therapeutic target and/or biomarker in GB patients.

Transforming Growth Factor-Beta (TGF-β)

TGF-β is associated with several functions in the organism, including homeostasis and embryonic development.[60] TGF-β plays a determinant role in the CNS, from embryonic development to inflammation in health and diseases in adulthood and aging.[61] It has been described that TGF-β can play a dual participation in cancer development; at the beginning of tumor development, TGF-β functions as tumor suppressor exerting, cell differentiation, apoptosis, and antiproliferative responses. Nevertheless, when the tumor is established, TGF-β functions as a cancer promoter, exerting several characteristics such as inducing epithelial-to-mesenchymal transition, evasion of the immunological system, and promoting the conditions for tumor spreading.[62–64]

GB can secretly TGF-β and activate a loop of autocrine stimulation, and it has been described that TGF-β has a role in the invasiveness stimulation in the GB cell lines. It was shown that induction of downregulation of TGF-beta type II receptor (TβRII), with small interference RNA in T98G, reduced invasiveness and migration after TGF-β stimulation in vitro.[65] Additionally, in GB U87 cells, TGF-β induced EMT markers expression, suggesting invasiveness stimulation on this GB cell line (Figure 1).[66] Additionally, it has been described that in the human brain endothelial cells, treatment with GB cell line U87 conditioned media induced the production of insulin-like growth factor-binding protein 7 (IGFBP7), a hallmark of GB endothelial cells, associated with angiogenesis. And, pretreatment with m1D11, a TGF-β neutralizing antibody, or SB431542, a TGF-β antagonist, blocks IGFBP7 production after conditional media treatment.[67]

Another source of TGF-β can proceed from the immunological component of GB-TM. It was shown that in an in vitro model using GL261 and CT-2A, mouse GB-like cells, TGF-β is secreted, which recruits macrophages; moreover, in this microenvironment, macrophages are led to a pro-tumoral phenotype that promotes angiogenesis.[68] Additionally, co-cultured U251 GB cell lines and macrophages induce macrophage TGF-β secretion, increasing migration. Furthermore, TGF-β1 treatment was enough to cause similar effects on U251 cells, while in the presence of SB431542, a TGF-β inhibitor, migration was decreased.[69] Another critical component of the GB-TM is regulatory T cells (Tregs), which participate in tumor immunologic surveillance evasion (Figure 1). It has been described that infiltration of Tregs was decreased by using the antibody m1D11, anti-TGF-β, in a GL261 mice model.[70] Together, these results suggest that TGF-β is critical in GB progression, regulating immunological surveillance and promoting a proangiogenic environment.

Sexual Hormones in Glioblastoma Tumor Microenvironment

It is well established that GB is more frequent in men than in women; this fact suggests an influence of sexual hormones on tumor development and progression.[71] The AR is over-expressed in GB cells, and androgens induce GB cell proliferation, migration, and invasion.[13] In sharp contrast, estrogens, mainly through estrogen receptor α (ERα), exhibit protective effects and may enhance treatment responses.[72] Then, in this section, we describe the knowledge about sexual hormone's effects on GB development and progression.

Androgens

Androgens are a group of steroid hormones involved in the production of secondary sexual characteristics in men. Androgens exert their function through the AR, a 110 kDa protein typically found in an inactive state coupled to chaperones such as HSP27, HSP40, and HSP70. When the AR comes into contact with its ligand, usually T, or its reduced metabolite, dihydrotestosterone (DHT), it causes conformational changes that allow its release from chaperones, subsequent dimerization, and translocation to the nucleus, where it plays its role as a ligand-activated transcription factor.[73] AR overexpression is associated with the development of certain cancers sensitive to sex hormones, such as prostate and breast cancer. Recently, it has been associated with the development and progression of GB.[74] Several studies suggest that T promotes the aggressiveness of GB. It has been reported that there are significant differences in serum T levels in patients with various types of gliomas compared with healthy subjects. T levels were higher in patients with glioblastoma than in healthy subjects.[75] Similarly, it was observed that those patients with GB who have androgen deficiency have a better prognosis, suggesting a potential role of T in the progression of this tumor.[76] In in vitro models, T and DHT can promote proliferation, migration, and invasion of different human glioblastoma-derived cell lines (Figure 2A).[15] Additionally, these cells express crucial proteins

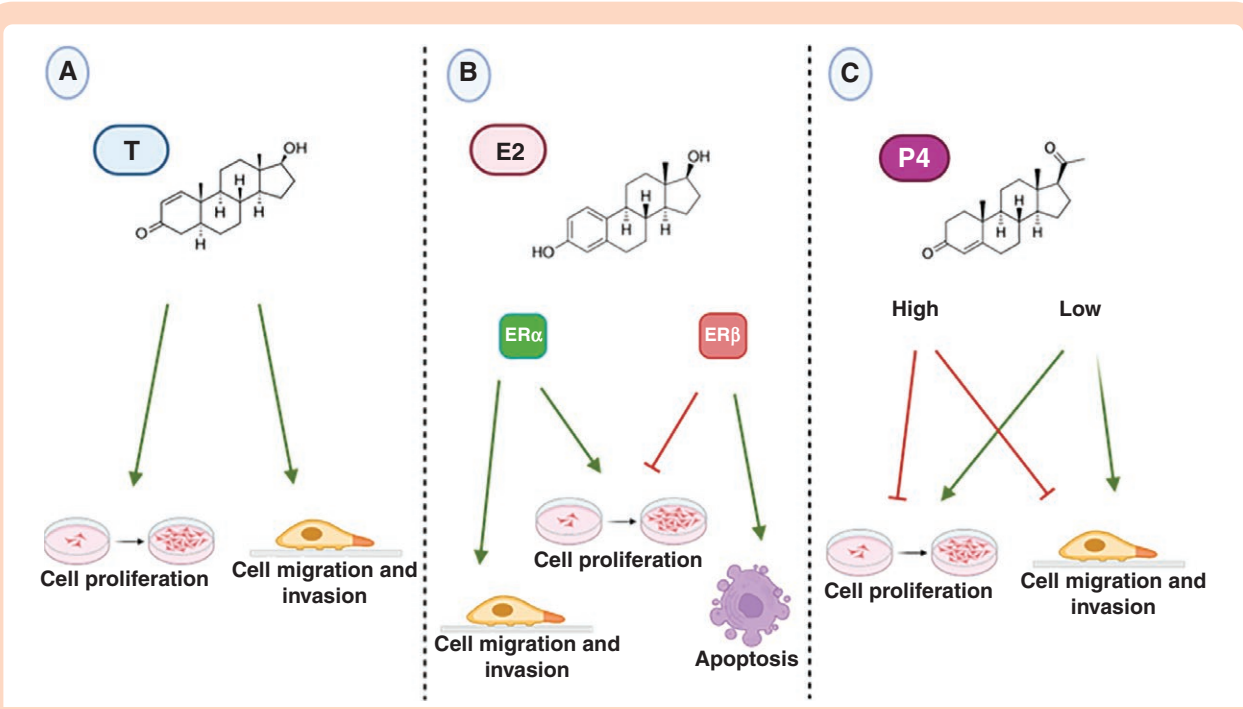

Figure 2. Sex hormones in GB-TME. Sex hormones can regulate different processes in GB cells. (**A**) Testosterone **(T)** can increase GB cell migration, proliferation, and invasion through its receptor AR. (**B**) Estradiol **(E2)** effects differ depending on which receptor **(ER)** is activated; ERα induces GB cell migration, proliferation, and invasion (arrow); in sharp contrast, ERβ induces GB cell apoptosis (arrow) and decreases proliferation (inhibitor). (**C**) Progesterone **(P4)** has a dual effect depending on the concentration; high levels (inhibitor) of P4 decrease GB cell proliferation, migration, and invasion. On the other hand, low levels (arrow) of P4 increase these processes in GB cells.

for androgen synthesis, such as 3β-HSD, 17β-HSD, and 5α-reductase.[77] In agreement with previous reports, at clinical and experimental levels, a higher expression of AR has been reported in tumor tissue compared to healthy brain tissue, and its presence has been observed in different cell lines derived from glioblastoma.[75,78] A correlation between receptor overexpression in tumor samples and a worse diagnosis was found.[79] In preclinical studies, AR inhibition, either by silencing or by pharmacological treatments using bicalutamide or enzalutamide, T antagonists, demonstrated a significant decrease in cell proliferation in vitro and in vivo, as well as the activation of caspases and the consequent generation of apoptosis.[78] Treatments with enzalutamide also demonstrated the ability to reduce the population of cancer stem cells present in the culture, generate neurospheres in vitro, and promote the expression of stemness-associated factors.[80] Similar results were observed with finasteride, an inhibitor of the 5α-reductase.[81]

Interestingly, there is evidence that AR can interact with other signaling pathways in GB. Since it is a tumor characterized by EGFR overexpression, a positive correlation was found between EGFR and AR expression. This study suggests that EGFR/Akt pathway activity favors the phosphorylation of residues S210 and S213 in AR, promoting its activation and translocation to the nucleus.[82] Additionally, it has been reported that activation of the TGFβ receptor inhibits the proliferative activity mediated by AR activation due to a direct interaction between the phosphorylated form of the AR and SMAD3.[83] In addition to the interaction of AR with signaling pathways such as EGFR/Akt and TGFβ/SMAD, in other cancer models, the AR can interact with other pathways such as Wnt/β-catenin, as well as with other sex hormone receptors; however, experimental evidence is needed to verify these interactions in GB cells. Taken together, current evidence suggests a strong involvement of the androgen/AR in the generation and maintenance of glioblastoma; however, the precise mechanisms and signaling pathways involved after AR activation are unclear.

Estrogens

GB is a tumor that more frequently occurs in men than in women, which has suggested a possible protective function of female sex hormones in GB.[71] In the case of E2, experimental evidence has shown that this hormone can have antitumor and pro-tumor effects. E2 usually functions through the estrogen receptors ERα and ERβ, identified in tumor samples and cell lines derived from GB.[84,85] As mentioned in the previous section, T promotes tumor growth in an AR-dependent manner; however, in tumor samples, the expression of the aromatase enzyme, responsible for metabolizing T into E2, has been found.[86] In different cell lines derived from human GB, there is evidence that E2 can increase cell growth and favor tumor progression, promoting cell proliferation, migration, and invasion processes at concentrations ranging from 5 to 10 nM.[87,88] It has been proposed that ERα mediates this effect; in the D54 human GB-derived cell line, the treatment

with E2-induced cell proliferation and the co-treatment with ICI 182, 780, an ER antagonist, blocked the proliferative effect of E2 in the D54 cell line (Figure 2B). Additionally, the treatment with PTT, an ERα agonist, increased the proliferation of D54 cells. In contrast, the treatment with DPN, an ERβ agonist, D54 cell proliferation was not affected.[89] Furthermore, it has been reported that E2 promotes epithelial-mesenchymal transition in U87 and U251 cell lines, modifying cell shape and size and inducing the expression of vimentin and E-cadherin, 2 important mesenchymal markers.[85] Besides, it has been described that E2 promotes resistance to temozolomide (TMZ) resistance, one of the most commonly used chemotherapeutic agents in GB treatment. In GB TMZ-resistant cells, E2 induced the increase of superoxide dismutase, catalase, and nuclear factor erythroid 2-related factor (NRF) 2 expression, regulating the oxidative stress in GB cells.[90]

Contrary to ERα pro-tumoral effects, ERβ activity has been associated with a better response to TMZ treatment in mice and cellular models. ERβ overexpression on U251 and U87MG induced downregulation of DNA damage response-related genes. Additionally, it has been reported that ERβ over-expressing U251 and U87MG cells exhibit high sensitivity to TMZ treatment compared to the control cells. Finally, in an orthotropic mouse model, ERβ over-expressing U251 and U87MG cells transplanted to the animals have shown more sensitivity to TMZ treatment than the control, which results in increased animal survival. Together, these experimental data suggest that ERβ can potentially enhance response to TMZ treatment in GB cells.[91] In addition, the ERβ agonist, LY500307, decreased cell growth and increased apoptosis in in vitro and in vivo models. LY500307 increased apoptosis in U251 and U87MG cell lines. Furthermore, LY500307 induced downregulation of DNA damage-related genes. The treatment with LY500307 in an orthotropic mouse model reduces tumor progression compared to animal controls. These results suggest that LY500307 inhibits the GB progression in in vitro and in vivo conditions by inducing apoptosis (Figure 2B).[92] ERβ overexpression, or the LY500307 treatment, was also associated with reduced stemness of glioma stem cells, lower capacity for neurosphere generation and self-renewal, and down-expression of stemness markers, such as CD133 and SOX2.[93] Then, the experimental evidence suggests that ER exerts a dual role in GB progression; the pro- or antitumor actions of E2 depend on the activation of ERα or ERβ, which shows potential for a therapeutic way to increase the patient's life span.

Progesterone

P4 and its receptor (PR) have been associated with pro- and antitumor processes. As has been observed with other sex hormone receptors, tumor samples from patients with gliomas of different malignancy grades, including GB, express PR both at the mRNA and protein levels.[94] It is now known that P4 concentration plays a critical role in regulating the growth and maintenance of GB cells. It has been reported that treatments with high concentrations of P4 (20–80 μM) decreased cell growth and viability in different GB cell lines. Interestingly, the opposite result was observed when low concentrations of P4 (0.1–10 μM) were administered (Figure 2C).[95] In the D54 and U373 cell lines, P4 treatments at concentrations of 10 nM promoted cell growth, and the P4 antagonist, RU486, prevented P4 effects.[96] Administration of the same P4 concentration increased cell migration and invasion processes in the D54 and U251 lines, reinforcing the idea that P4 promotes tumor malignancy processes at low concentrations (Figure 2C).[97] PR expression was found in primary and secondary neurospheres in suspension culture models. Neurospheres showed increased cell growth when treated with P4, indicating that P4 and PR are involved in maintaining stemness in GB cells.[98] Besides, in a rat model, activation of the intracellular PR promoted tumor growth and a greater area of infiltration in the brain parenchyma; silencing PR expression prevents P4 effects.[99] Interestingly, in addition to the action of the intracellular receptor, membrane PR (mPR) has also been reported in different human cell lines derived from GB, and their expression level can be regulated by P4 and E2.[100] In U87MG and U251 GB cell lines, the treatment with the mPR agonist, Org OD 02-0, increased cell proliferation, invasion, and migration.[101] This suggests that intracellular and mPR promote malignant processes in GB cells. As mentioned above, P4 concentrations are crucial in determining whether a pro- or antitumor effect will be exerted. In the case of high hormone doses, there is evidence that P4 exerts antitumor effects; it was reported that the antitumor effects of P4 were due to an increased expression of pro-apoptotic proteins, as well as a decrease in the PI3K/AKT/mTOR signaling pathway, reducing tumor growth.[95] Treatment of U87MG and U118 with P4 and TMZ-induced tumor cell death in a dose-dependent fashion. High doses of P4 produced more cell death than TMZ alone. Additionally, when combined, P4 enhanced the cell death-inducing effect of TMZ. P4 alone and with TMZ suppressed the EGFR/PI3K/Akt/mTOR signaling pathway in U87MG cells, thus suppressing cell proliferation. P4 and TMZ individually reduced cell migration in U87MG cells, but the combined effect was higher.[102] Additionally, treatments with high concentrations of P4 may have an action on mitochondrial balance, showing a lower rate of cellular respiration as well as a lower activation of the glycolysis pathway, suggesting that the antitumor action of P4 may be partly due to a direct action on cellular metabolism.[103] Finally, despite the current experimental evidence, further research is needed to clarify the mechanisms involved in P4-mediated tumor regulation and determine whether its action in anti- or pro-tumoral effects can be mediated by its canonical receptors or the interaction with other signaling pathways.

Crosstalk Between Cytokines and Sexual Hormones in Glioblastoma

As described above, cytokines and sex hormones (Figure 3) are critical in GB development, establishment, and progression. However, information about the intercommunication between hormones and cytokines via target cells has yet to be fully described. This section summarizes the

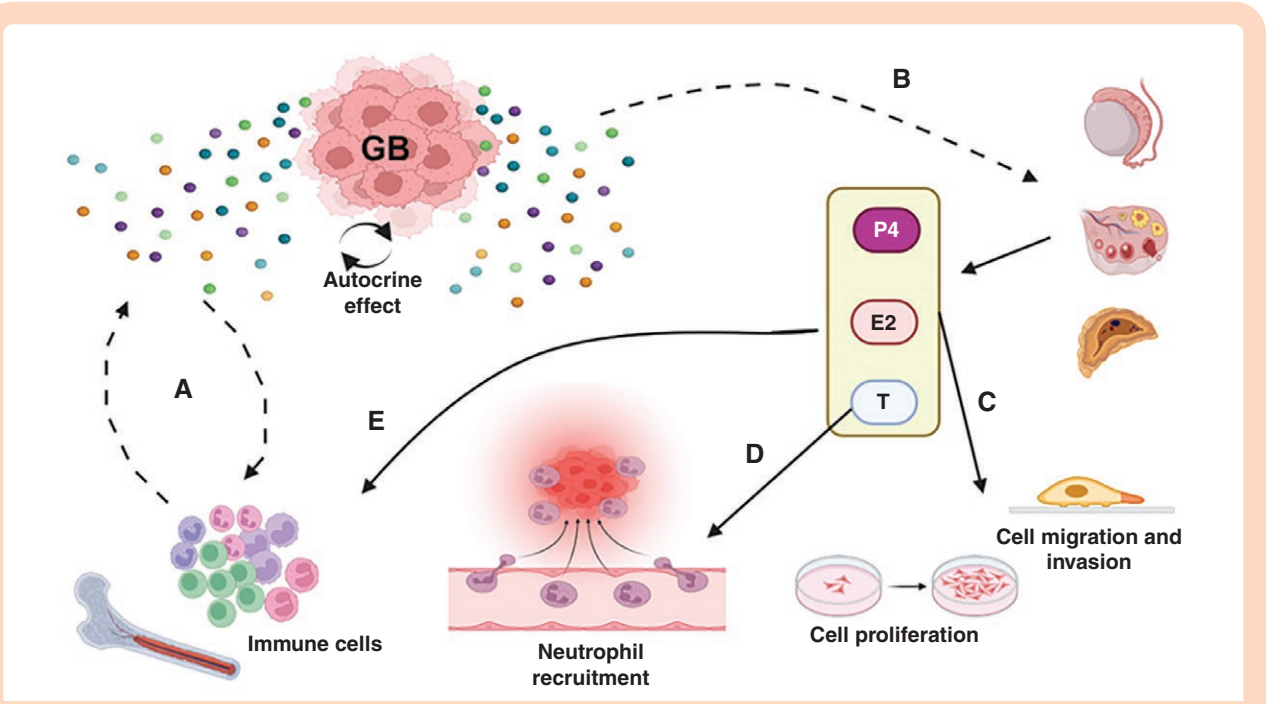

Figure 3. Crosstalk between cytokines and sex hormones in GB-TM. Cytokines and sex hormones affect GB progression. (**A**) Inflammation in the tumor microenvironment induces immune cell recruitment and influences GB development and progression. (**B**) In a paracrine response to an inflammatory environment, GB cells can secrete more cytokines, which could influence sex hormone production, as described in other conditions. (**C**) In turn, sex hormones can influence GB cell proliferation, migration, and invasion. (**D**) Additionally, testosterone **(T)** regulates neutrophil recruitment to the site of inflammation. (**E**) **T**, Estradiol **(E2),** and progesterone **(P4)** can influence immune cell development and responses.

knowledge about the cytokines-hormones axis in the GB context.

In general, androgens have been described as negative regulators of immune response; nevertheless, this postulation is not equal for all immune cells.[104] AR is expressed in lymphoid and myeloid cells in the bone marrow; however, it is not expressed in mature lymphocytes. Then, it has been proposed that androgens are essential in lymphocyte maturation (Figure 3).[105] In neutrophils, the most abundant leukocytes in the bloodstream, androgens have been described as acting not only in development but also in the regulation of neutrophil functions. It has been described that in a melanoma mouse model, neutrophil counts in orchiectomized mice were reduced.[106] Furthermore, in a mouse model of prostate inflammation, it has been shown that neutrophil recruitment increases in androgens-treated animals compared to the control animals (Figure 3). However, mice neutrophils exposed to large amounts of androgens were less efficient in bactericidal ability and secreted more anti-inflammatory cytokines than control mice.[107] All this evidence shows that androgens can play different roles depending on the immune cells. However, the role of androgens in human GB immunity is unclear. In the U87MG GB cell line, activation of TGF-β signaling significantly inhibited cell growth, and apoptosis was increased. Moreover, DHT, an AR ligand, decreased the effect of TGF-β on growth and apoptosis, suggesting that the AR signaling pathway may have interfered with the TGF-β signaling in U87MG cells. However, DHT did not affect the total protein nor the phosphorylated protein of SMAD3. This major TGF-β signaling downstream effector suggested that AR activation does not affect the SMAD3 protein production or phosphorylation of the TGF-β receptor and SMAD3. Finally, immunoprecipitation followed by immunoblot confirmed binding of pAR to pSMAD3, which may inhibit the DNA binding of pSMAD3 and subsequently prevent its effect on cell growth in U87MG cells. This data suggests that AR signaling may promote tumorigenesis of GB in adult men by inhibiting TGF-β signaling.[83] However, a recent study under review from Lathia et al. that employed the SB28 and GL261 mouse GB cell model has shown that the absence of androgens promotes an immunosuppressive environment, mediating tumor progression. Additionally, this study describes that in the presence of the brain tumor and deprivation of androgens, T-cell dysfunction was observed, leading to accelerated tumor growth. These results suggest an immunoprotective role of androgens in mice tumor brain models.[108] Then, it is essential to confirm these results by employing human GB cell lines in future studies since the behavior of the mice brain tumor model could present variations compared to brain tumors in humans.

As described above, estrogens influence GB establishment and progression (Figure 3); however, how estrogens regulate the immune response in the GB context needs to be defined. E2, through their receptors ER-α and ER-β, can regulate both innate and adaptative immune responses; ER-α and ER-β are expressed in different immune cells, including lymphocytes, monocytes, macrophages, neutrophils, dendritic cells, and NK cells.[109] Estrogens participate in immune cell development and influence immune

cell functions; for example, depending on the cellular context, E2 regulates type I INF secretion or suppresses pro-inflammatory cytokine secretion (Figure 3).[110] In pro-inflammatory conditions, E2 increases MHCII expression in dendritic cells, M1 macrophage polarization, neutrophils respiratory burst, B cells antibody production, and Th1 polarization response. In anti-inflammatory conditions, E2 induces dendritic cell tolerance, M2 macrophage polarization, neutrophil extracellular trap production, and Th2 polarization response.

The differential expression of ER could explain the dimorphic nature of immunity: females generally show better immune responses than males.[111] It has been described that a relationship exists between E2 and TGF-β signaling pathways and how this axis affects epithelial-mesenchymal transition in human GB cells. E2 and TGF-β reduce ER-α and Smad2/3 expression. TGF-β produces Smad2 phosphorylation flowed off its nuclear translocation, while E2 is inhibited. Additionally, TGF-β and E2 induced cellular changes related to the epithelial-mesenchymal transition, such as morphological changes, actin filament reorganization, and mesenchymal markers (N-cadherin and vimentin) expression. Finally, it was described that the co-treatment of E2 and TGF-β blocked epithelial-mesenchymal transition activation. Together, these data suggest that E2 and TGF-β signaling pathways interact through ER-α and Smad2/3 mediators in cells derived from human GB and inhibit epithelial-mesenchymal transition activation induced by both factors separately.[112]

Additionally, P4 could participate in GB progression (Figure 3); however, more investigation is needed to describe its effects. It has been described that P4 has significant immunomodulatory roles that regulate innate and adaptive immune responses. P4 effects are substantial during pregnancy but extend to various physiological processes influenced by hormonal fluctuations; it is well-described that P4 has immunosuppressive effects, a crucial event to maintaining pregnancy, by avoiding maternal immune rejection of the product. P4 induces Th2 polarization, inducing anti-inflammatory cytokine secretion, such as IL-10, and suppressing pro-inflammatory, such as TNF-α (Figure 3).[113,114] PRs are expressed in immune cells such as lymphocytes, dendritic cells, macrophages, and neutrophils. Activation of PRs interferes with NF-κB signaling, a pathway crucial to modulating pro-inflammatory cytokine secretion (Figure 3). Furthermore, it has been shown that P4 can suppress NK cells and macrophage cytotoxic activity.[115,116] As described, P4 can modulate immune response and influence cytokine secretion by GB and immune cells that polarize immune response to promote tumor establishment and progression; however, the effect of progestins in the GB context has not been explored.

It has been described that cytokines can regulate steroidogenesis at different levels. Macrophages and lymphocytes can infiltrate the adrenal cortex, and adrenocortical and chromaffin cells produce cytokines, such as IL-1, IL-6, TNF-α leukemia inhibitory factor, and IL-18, which have a vital role in the immune-adreno-cortical communication.[117] In addition to cytokines interacting with adrenal function, cytokine-independent mechanisms are responsible for cell-to-cell-mediated immune regulation of the adrenal gland (Figure 3).[118] Additionally, it has been described that lymphocytes stimulate androgen production at the adrenal level. In the co-culture of T lymphocytes and adrenocortical cells, T lymphocytes increase the dehydroepiandrosterone production of adrenocortical cells compared with the controls in a direct cell–cell contact fashion.[119] Moreover, macrophages can regulate steroidogenesis by influencing Sertoli cell activity and germ cell survival in human testes. In rats, IL-1 is involved in the paracrine regulation of Leydig cell steroidogenesis (Figure 3).[120] Furthermore, high levels of IL-6 have been shown to affect male response to luteinizing hormone in Leydig cells to activate steroidogenesis (Figure 3). The mechanism that guides this IL-6 effect involves the JAK/STAT pathway activated by the corresponding IL-6 receptor.[121] Additionally, a high concentration of TNF-α decreases the expression of the steroidogenic acute regulatory protein (StAR), CYP11A1, CYP17A1, and HSD3B key enzymes to process cholesterol and produce not only T but also other steroid hormones.[122]

In females, cytokines participate in follicular development, atresia, ovulation, corpus luteum function, and steroid production. Leutinizing hormone induces IL-8 and monocyte chemotactic protein-1 (MCP-1) expression in the antral phase. IL-8 and MCP-1 recruit neutrophils and monocytes to the preovulatory follicle. These events are crucial to remodeling and degrading the tissue to allow follicular rupture.[123] In granulosa cells, cytokines regulate steroid hormone production (Figure 3); IL-6 is produced in response to gonadotropins, which enhance the production of steroid hormones necessary for ovulation and luteinization.[124] Finally, Immune cells can synthesize steroid hormones. For example, macrophages can process androstenedione into androgens, which regulate the local steroidogenesis and phagocytic activity.[125] Furthermore, it has been shown that monocyte-macrophage cells can produce steroids locally in the TM in mouse colorectal cancer models, increasing T lymphocyte dysfunction.[126] All these data suggest an elegant and complex relationship between immune system function and hormonal regulation that a minimal disruption could end in disease development such as GB or another type of cancer.

Conclusions

This review summarizes that GB-TM regulates a complex communication web in which cytokines and sex hormones are critical in promoting tumor establishment and progression. Too much to do is needed to offer alternatives to the treatment of GB patients; however, in our view, understanding immunoendocrine communication provides an opportunity to propose alternatives in GB treatment by influencing this critical communication axis in the future; it is crucial to focus efforts on developing investigations in this field, trying to answer the questions: How does the endocrine environment affect immune cell recruitment to GB-TM? In GB-TM, do immune cells locally contribute to steroid production? Does cytokine secretion by GB cells in TM affect steroidogenesis, and does this event affect GB establishment and progression? Is cytokine and sex hormone communication different in females and males in the GB-TME context? All these questions

could open the possibility of acquiring knowledge of GB biology and offer new options in GB therapy.

Keywords

cytokines | glioblastoma | immunoendocrine communication | tumor microenvironment | sex hormones

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The authors declare no conflict of interest.

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O. R. A. prepared the conceptualization, primary draft, and figures. J. C. Q. helped in the primary draft, and I.C.A. made comments and revisions.

Data availability

Not applicable.

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