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REVIEW

Reproductive epidemiology of glial tumors may reveal novel treatments: high-dose progestins or progesterone antagonists as endocrino-immune modifiers against glioma

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Abstract

Female gender, contraceptives, and menopausal hormone replacement treatments containing progesterone analogues associate with higher risk of meningiomas yet with lower risk of gliomas. Progesterone receptor (PR) expression and mifepristone treatment was highly discussed for meningiomas. However, much less is known in regard to progesterone actions in gliomas despite PR expression strongly correlates with their grade. Meningiomas and gliomas may grow faster during gestation; but paradoxically, parousity reduces lifetime risk of gliomas which can be explained with dichotomous cell growth-stimulating and inhibitory actions of progesterone at low versus high levels. Progesterone levels gradually increase in gestation up to 200-fold and the incidence of highly angiogenic brain tumors decreases in the last trimester. Indeed, progesterone stimulates glial tumor cell growth at low doses (10 nM) while induces cell kill at higher doses. During gestation, some immune pathways are activated to protect the mother and the fetus against microbial pathogens. In parallel, high-dose medroxyprogesterone acetate (MPA) used in treatment of endometrial carcinoma decreases tumoral expression of PR-B and increases infiltration of cytotoxic T lymphocytes and natural killer cells. MPA also synergies with IL-2 in clinical treatment of renal cancer. In both glioma and meningioma, the dominant cytosolic PR is PR-B which increases cell growth, while PR-A limits cell growth. This seems also paradoxical at the first glance due to opposite behavior of these tumors in diverse endocrine conditions. High-dose progestins may inhibit brain tumor growth by downregulating PR-B, yet the dosage thresholds may differ between glial and meningeal tumors due to higher total PR expression in meningiomas. Supporting this proposal, certain progestins were reported to stimulate meningioma growth in anecdotal reports, but same agents at much higher doses reduced meningioma cell proliferation in pilot clinical studies. PR antagonist mifepristone reduced meningioma growth in some clinical studies, but lacked efficacy in others. In fact, mifepristone also has partial PR agonist efficacy and acts in synergy with MPA to block EC growth. Hence, a similar mechanism of receptor downregulation may also account for mifepristone. Both MPA and mifepristone also harbor myeloprotective features against chemotherapy. Ulipristal is another contraceptive PR antagonist and exerts promising anticancer activity on drug-resistant ovarian cancer and BRCA1-mutant breast cancer cells, which can be tested in animal glioblastoma models. We propose that progestins strongly deserve to be investigated in experimental models of glioblastoma alone and in combination with immunostimulating agents.

Keywords Progesterone receptor · Medroxyprogesterone acetate · Gliomas

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Introduction

The glioma problem, embryonic mimicry of malignancies, and progesterone

Gliomas are the most frequent primary malignant brain tumors, accounting for approximately 80% of cases [67]. Gliobastoma multiforme (GBM) is the most common aggressive glioma [67]. Despite vaste number of basic studies, the

prognosis of high-grade glial tumors is very poor. Hence, development of new treatment concepts is of urgent need. To achieve this goal, repurposal of known drugs used in different indications may also be helpful. A plausible approach could be revaluation of the "embryonic/placental mimicry concept" of cancer [34, 110]; and targeting tumoral embryonic mimicry with endocrine agents and immunotherapy to block this mimicry. We were the first to show that progesterone analogue medroxyprogesterone acetate (MPA) blocks growth and induces chemotherapy sensitization in glioma cells [4, 5]. In this review, we propose that high-dose progestins or antiprogestins may block embryonic mimicry of brain tumors and lead their differentiation and apoptosis via progesterone receptor (PR)-downregulation and inducing tumor-specific immunity.

Progesterone (Fig. 1) is a cycling ovarian steroid hormone and has a major role to promote endometrial glandular differentiation. Antigenic tissue is tolerated by an intact immune system in two biological situations, pregnancy and malignancy, and many evidences support that similar immune mechanisms may be responsible for the tolerance of antigenic tissue in these two conditions [45]. This evidence is based on a number of common features, including embryonic protein expression of neoplastic tissues and common lymphocyte populations in pregnancy and malignancy [45]. Pregnancy is a unique period, where progesterone concentrations gradually increase up to 200-fold [64]. The gestational process involves rapid cell proliferation and low cell differentiation at early stages, which progresses with reduced cell proliferation and increasing cell differentiation at later periods.

Similar processes occur for angiogenesis, intense angiogenic pathways are activated in the mothers' womb to provide a stable adhering of placental tissue at the onset of pregnancy. On the other hand, reduction of cell proliferation and gradual apoptosis of endothelia is necessary for regression of placental vessels to avoid severe uterine bleeding during placental separation at parturition. Hence, it is not surprising to discover that low levels of progesterone stimulate cell growth and angiogenesis in cancer cells [15], while higher levels induce cell differentiation and block angiogenesis [1, 63, 77]. Similarly, MPA (Fig. 1)—a commonly used 17-OH progesterone analogue—could provide maintenance of pregnancy at luteal insufficiency [52], yet it is being used for depot contraception at higher doses [33]. As will be discussed below, some highly angiogenic brain malignancies manifest with a higher incidence during the first trimester, while their incidence continuously declines at later stages of gestation [99]. It was also shown that manifestation of gliomas associates with the first trimester, whereas meningiomas are more frequently observed in the second and third trimester [99].

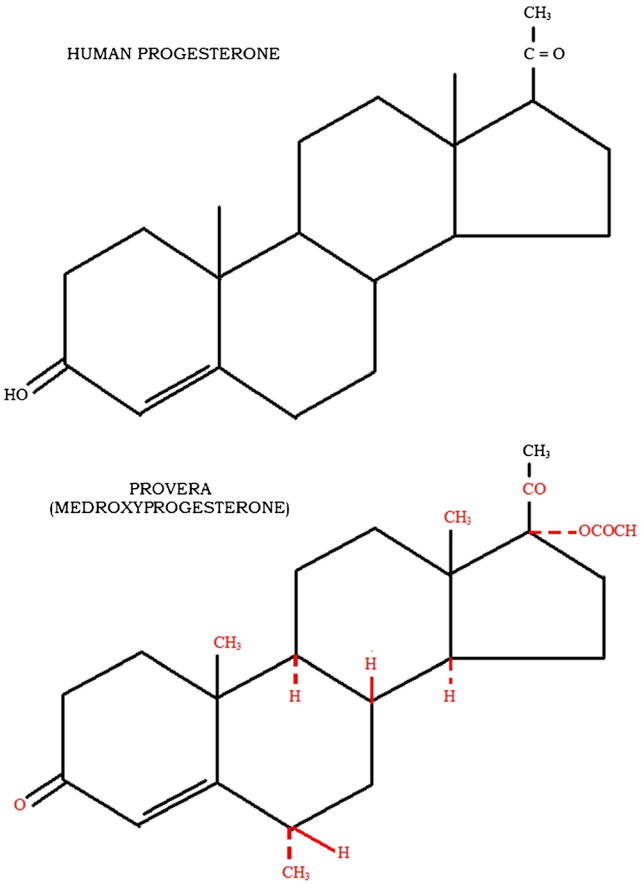

Fig. 1 Progesterone

Similarly, while low-dose MPA may enhance risk of breast cancer in hormone replacement treatment (HRT) [39], much higher doses of MPA induce clinical regressions in breast [3, 70], renal [87], and endometrium cancer [122]. Despite pregnancy is discussed mainly in regard to immune suppression to avoid immune rejection of the fetus, it is largely neglected that the immune system functions more efficiently in several contexts to prevent infectious threats against the mother and the fetus [89, 100, 105]. Similarly, despite MPA also binds glucocorticoid receptors and suppresses some immune responses, clinical observations suggested that it did not hinder—or in some instances augmented—cancer treatments including immunostimulants and chemotherapy [35, 76, 120]. We propose that progesterone and its analogues may increase glial tumor cell proliferation at low dosages, but induces cell differentiation and cell death at higher dosages and with prolonged exposure as observed in breast cancer [74]. A similar situation may exist in meningiomas, but a higher dose range of progesterone may act proliferative on these tumors, since they manifest in later stages of gestation, as suggested above [99]. We also propose that progesterone antagonists and high-dose progestins may act via similar mechanisms in eliciting

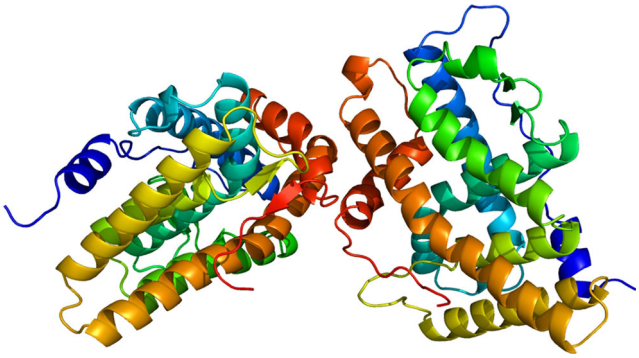

Fig. 2 Progesterone receptors

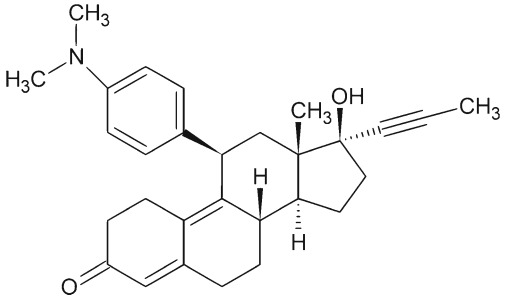

Fig. 4 PR antagonist mifepristone

proliferation arrest and death of brain tumor cells via downregulation of proliferative progesterone receptors (PRs, Figs. 2 and 3).

Several observations of ours and others strengthen this proposal. Following our first published observations that MPA is capable to reduce clonogenicity and to increase chemotherapy efficacy in rat glioma cells [4,5], we consistently observe that MPA increases growth of human glioma cells at low doses, yet inhibits growth and invasion of human glioma and meningioma spheroids at higher dosages [unpublished data]. These are parallel to published findings of other research groups in the context of gliomas [10, 11] and meningiomas [79, 80, 118]. Some authors proposed that progesterone at low doses stimulates glial tumor growth via PR but at high dosages suppresses growth independent of PR, since a PR antagonist mifepristone (Fig. 4) hinders proliferative effects of progesterone at low dose but has no influence on the effects of progesterone at high dosages [10, 11]. However, there exist studies that mifepristone may also act as a PR agonist [83] and even potentiate antitumor effects of MPA [85, 86]. Hence, the antitumor efficacy of antiprogestins and progestins at high doses may occur via shared mechanisms. Below, we will provide epidemiological and molecular clues in regard to actions of progesterone and its analogues (progestins) in glial tumors.

Effects of gender, oral contraceptives, and hormone replacement therapy on the risk of glial tumors

In adults, the incidence of glioma is about 50% higher in men than in women; the age-adjusted annual incidence rate of glioma in the USA is 7.6 in 100,000 in males and 5.4 in 100,000 in females, and the male-to-female excess is stable over time [67]. Moreover, the rate ratio for GBM in women in comparison to men begin to decline throughout the pre-menopausal years, reaching to 0.51 in the age interval 50–54 years [67]. Thereafter, the rate ratio increased and remained at a constant level of about 0.65 in parallel to decreasing levels of female hormones [67]. These findings strongly suggest that female hormones have some preventive effects on gliomagenesis. In 2011, Cowppli-Bony et al. published their review study regarding role of steroid hormones in brain tumors. They revealed that the most consistent results were a decrease in glioma risk in everparous women or in women treated by post-

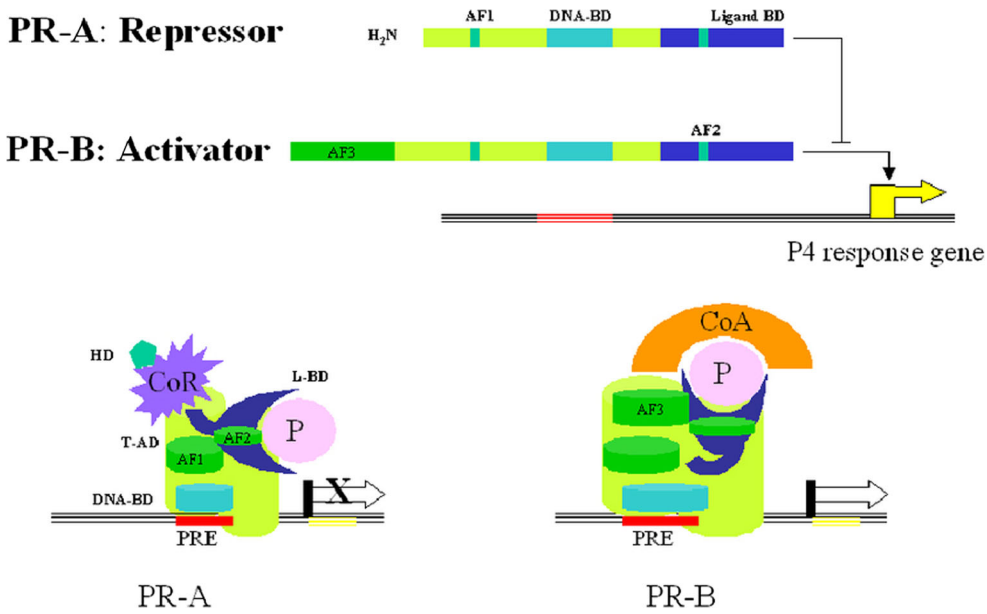

Fig. 3 Isoforms PR-A and PR-B. Source: Goldman S, Shalev E. Progesterone receptor profile in the decidua and fetal membrane. Front Biosci. 2007 Jan 1;12:634–48

menopausal hormone replacement therapy (HRT regimes contain mostly progestins with estrogens and rarely single estrogens) and contraceptives (contraceptives always contain progestins) [31]. Other consistent results included increase in glioma risk for women with late menarche or in menopausal women (shorter or reduced exposure to female hormones) and an increase in risk of meningioma with HRT in opposite to gliomas [31].

In investigations which studied the assocation of oral contraceptives (OC) with glioma, exposure was frequently assessed by "yes/no", and less so duration of treatment was considered. According to the review of Cowpli-Bonny, seven of such studies showed a lesser glioma risk in OC users [31], from 7 to 34%, significant in two studies [37, 56]. This result was consistent with the significant 35% decrease in risk found in another study that analyzed the overall role of hormonal therapies (OC and/or HRT) [103]. Duration of use did not seem to play a profound role [16, 56, 67, 107]; except in one study in which the use for 10 years or more was associated with a 52% reduction in glioma risk [37]. It was also reported that current use of OC was more protective than the past use (OR = 0.3 versus OR = 0.8) [37].

Benson et al. reported higher risk of gliomas with HRT. But interestingly, when overviewing their results, it becomes clear that their results showed enhancement of risks in HRT regimes, which contain only estrogens. Their investigation consisted of a large prospective study including 1,147,894 post-menopausal women analyzed during the Million Women Study [16]. Among current users of HRT, there was significant heterogeneity by the type of HRT. The users of estrogen-only HRT had higher risk of all central nervous system (CNS) tumors than users of estrogen-progesterone HRT (RR = 1.42 versus RR = 0.97) (heterogeneity $p < 0.0001$) [16]. When subgroups were analyzed regarding the specific progestin constituent of HRT, the RRs for glioma incidence were 1.08, 0.85, and 0.69 for norethisterone, norgestrel, and MPA, respectively [16]. The risk reduction by MPA in a study, which showed excess risk with HRT, was a noteworthy finding.

Many investigations found decreased risk of glioma in women using HRT, taking into consideration of the post-menopausal status [16, 37, 56, 107 or not 62, 68]. The range of this decline, from 6 to 44%, was similar to that observed with OC use. A more protective effect for current HRT use compared to past use was found in one study (OR = 0.4 versus OR = 0.8) [37], while no difference between past and current use was found in two other studies [31]. Interaction between OC and HRT use was also determined in post-menopausal women [37]. Women having used HRT had a decreased glioma risk which did not differ whether they had previously used OC or not.

A Danish group published the findings of a nationwide nested case-control study on the association of HRT with the incidence of gliomas [6]. Overall, they showed no higher risk of gliomas with HRT usage, but they found that when HRT usage was longer than 10 years, estrogen only, progestins only but not combined estrogen-progestin regimes increased risk [6]. But their analyses defining the HRT use according to the duration of use revealed that the ORs were close to unity for all other duration periods ($< 1, \geq 1$ to $> 5, \geq 5$ to > 10). Moreover, while analyses gave similar estimates for HRT overall, estrogen-only and estrogen + progestin combinations, such analyses could not be performed for single progestins due to small numbers [6]. The publication did not also provide data on which specific progestins were associated with risks, since the androgenicity of progestins highly differs. In 2013, Qi et al. reported the results of their metaanalysis of 11 case-control studies regarding effects of exogenous and endogenous hormones on glioma [95]. The overall pooled RR of glioma for ever users versus never users of OC was 0.71, with low heterogeneity [95]. The cumulative risk estimates for ever users versus never users of HRT were 0.68, with low heterogeneity [95]. According to the age at menarche, the pooled RR for the oldest age group versus the youngest age group was 1.40, with high heterogeneity [95]. The findings of their metaanalysis indicated a lower risk for ever users of OC or HRT in comparison to never users, whereas older age at menarche was associated with a statistically higher risk of glioma [95].

Using national health registries in Denmark, Andersen et al. determined all women ages 15 to 49 years with a first-time diagnosis of pathologically proven glioma between 2000 and 2009 [7]. Each case was age-matched to eight population controls using risk set sampling. Based on prescription data, exposure until 2 years prior to the index date was grouped according to hormonal contraceptive type, i.e., combined estrogen-progestagen or progestagen only, and duration of use (< 1, 1 to < 5, ≥ 5 years). They identified 317 cases and 2126 controls [7]. Ever use of hormonal OCs was associated with an OR of 1.5 and the OR increased with duration of use (long term, ≥ 5 years OR 1.9). The association between long-term hormonal OC use and glioma risk was most pronounced for progestagen-only therapy (OR 2.4) [7]. In analyses in regard to histological type of glioma, slightly higher risks were observed for GBM. They underlined that a likely overlooked confounder could be obesity because of preferential prescribing of progestagen-only contraceptives to women who are overweight as recommended in the Danish drug manual [7].

Anic et al. analyzed the effects of reproductive on the risk of glioma and meningioma among women included 507 glioma, 247 meningioma, and 695 healthy controls [8]. An older age at menarche was associated with an increased risk of glioma (≥ 15 versus ≤ 12 years OR = 1.65), with a higher association witnessed in pre-menopausal (OR = 2.22) than post-menopausal (OR = 1.55) women [8]. In comparison to controls, glioma cases were less likely to be long-term users of

OCs (OR = 0.47) [8]. Long-term use of OCs (10 or more years) was inversely associated with glioma though not meningioma. Glioma cases were more likely to be nulliparous in comparison to controls and menopause was associated with a higher risk for meningioma [8].

Krishnamachari performed a pooled multisite analysis of pre- and post-menopausal women, studying the effect of female reproductive factors and hormonal drugs [71]. The analyses including both pre- and post-menopausal women determined 968 cases and 1322 controls. Menarche over the age of 15 as compared to under 12 was associated with a statistically higher risk for glioma (OR = 2.0). Use of oral OCs was oppositely associated with risk of glioma (OR = 0.61), and there was an inverse trend with longer duration of OC use (p for trend < 0.0001) [71]. Use of HRT was also oppositely associated with risk of glioma (OR 0.55), and there was an inverse trend with longer duration of use (p for trend < 0.0001) [71]. Moreover, in comparison to those declaring neither OC use nor HRT use, those who reported using both were much less likely to suffer from glioma (OR = 0.34) [71].

In 2015, Benson et al. reported results of a metaanalysis on HRT and brain tumor risk [17]. The metaanalyses demonstrated significantly enhanced risks for all brain tumors, glioma, and meningioma in users of estrogen-only; but not estrogen-progestin HRT and these risk modifications differed in a statistically significant manner [17]. The reason of the differences obtained from different epidemiological studies is not easily explicable. In certain contexts, effected by anthropometric parameters (e.g., obesity) or personal configurations in PR polymorphisms differentially dispersed in different populations, progestins may stimulate glial tumors. But an overview of the published data dominantly indicates that continous exposure to progestins mostly decrease of malignant glial tumors but enhances risk of meningiomas.

Accelarated growth of glial tumors during pregnancy but parousity protection against glial tumor risk: how can we explain this paradox?

First in 1984, Haas has reported reduced frequency of brain tumors among newly diagnosed cancer in correlation with gestation [53]. She analyzed cancer patients who were pregnant at the time of malignancy diagnosis by the National Cancer Registry (NCR) of the German Democratic Republic (GDR) for the years 1970 through 1979 [53]. A total of 355 such cases were determined in women aged 15–44, and during the same period, 2,103,112 live births were registered. Rank in order of decreasing frequency was cervix, breast, ovary, lymphoma, brain cancers, and leukemia. On the basis of general female population rates, 555.8 cancer cases were expected, giving a significantly reduced observed to expected ratio (O/E) of 0.64 [53]. On the other hand, the O/E for invasive carcinoma of the cervix was significantly elevated at 1.15. Very prominently, tumors of the brain occured at 0.38 times the expected frequencies, respectively. Pregnancy period associates with higher medical observation, and hence, the diagnosis of cancer cases might be expected to be higher [53]. Therefore, it is particularly important to find the lower frequencies of some cancer types observed in comparison to those expected [53].

Two years later, Haas reported the subtypes of brain tumors associated with pregnancy, which were reported to the NCR of the GDR from 1961 to 1979 [54]. Primary cerebral cancers in which the patient was pregnant at diagnosis was grouped according to ICD 191 and a total of 17 histologically confirmed brain cancers (nine astrocytoma, six GBM, one ependymoma, and one sarcoma) are detected in the pregnant patients in the GDR from 1961 to 1979, a frequency of 3.6 per 10^6 births [54]. From 1961 to 1969, the O/E ratio was 0.28, and from 1970 to 1979, the O/E ratio was 0.26 [54]. It should be taken into consideration that the reporting of cancers and benign tumors in the GDR was obligatory and also that the magnitude of the reduction in the O/E for brain cancers was so prominent that the artifacts were unlikely to be responsible of the observed decrease [54]. In contrast to other tumors, observed cases of acoustic neurinoma were not less frequent indicating that reductions of astrocytomas and GBMs was a specific finding [54]. Here, one could bring up the concern that brain tumor studies before the improved imaging modalities may be confounded and may not represent the prevalence of the disease. However, as will be outlined below, all other studies up to date demonstrated similar results.

In 1987, Roelvink reviewed 86 reports and determined 223 brain tumor cases associated with pregnancy and they found that manifestation of gliomas associates with first trimester of pregnancy, whereas meningiomas associate with second and third trimester of pregnancy [99]. They also outlined that gliomas with ≥ 5 fmol/mg of cytosolic PR constitute 40% and as with ≥ 10 fmol/mg of cytosolic PR constitute 20%, whereas meningiomas ≥ 100 fmol/mg of cytosolic protein PR constitute 94% [99]. Thus, meningiomas contain a much higher level of PR. Hence, intense doses of progestins or pure antiprogestins may be required in treatment of meningioma, since their high PR content may not be easily downregulated. Lambe et al. published a case-control study nested within a large nationwide cohort in Sweden [73]. One thousand eighty-eight patients with meningiomas and 1657 patients with gliomas were identified, and for every woman diagnosed with brain tumor, five age-matched controls were selected. Everparous women were found to have leseser risk of glioma in comparison to nulliparous, while parity was unrelated to meningioma [73].

Studies found a statistically significant decreased risk for women with at least one live birth compared to women without children [21, 73]. Trend with the number of children is not clear, but two studies showed a significant decreased risk for

women who gave birth to five children or more: Hatch [56] (OR = 0.45) and Lambe [73] (OR = 0.6). Further, Cantor noted a decrease in risk of GBMs is stronger than astrocytomas in multiparous women [21]. Wigertz et al. performed a case-control study of glioma ($n = 626$) and meningioma ($n = 906$) cases and determined controls in a randomized fashion ($n = 1774$) [121]. A decreased glioma risk was associated with ever pregnancy compared with never pregnancy (OR 0.8) [121]. In opposite, meningioma risk was enhanced among women younger than 50 years in association which gave birth to three children in comparison to nulliparous women; (p trend among parous women = 0.01) [121].

On the other hand, higher duration of breast-feeding among parous women increased the glioma risk (OR 2.2 breast-feeding 36 months or more compared with breast-feeding 3 months or less), indicating that pregnancy per se, but not prolactin played a role in reduction of glial tumor risk with pregnancy [121]. Rao has underlined a significant negative correlation between the levels of 17α-hydroxyprogesterone (17-OHP) and the appearance of highly vascularized brain and spinal tumors seen during pregnancy and proposed that 17-OHPs can be used as antiangiogenic steroids in treatment of brain neoplasms [96]. Since Roelvink suggested increased incidence of gliomas during the first trimester of pregnancy [99], it could be anticipated that low levels of 17-OHPs augment while higher levels reduce glioma angiogenesis. Overall, low dose of progestins during early pregnancy may induce faster progression of gliomas via increasing cell proliferation and angiogenesis. On the other hand, continuous exposure to and increase of progestins up to 160 to 200 μM at late gestation may differentiate glial cancer cells and block angiogenesis.

Molecular biochemistry of the cytosolic progesterone receptors

Progesterone receptors (PRs) (Fig. 2) are composed of a central DNA binding domain (DBD) and a carboxyl-terminal ligand binding domain (LBD) with multiple activation (AF) and inhibitory (IF) functional regions interacting with transcriptional coregulators [102]. In humans, the cytosolic PR is encoded by a single gene residing on chromosome 11q22 and its two distinct isoforms PR-A and PR-B (Fig. 3) are transcribed from a single gene from distinct promoters. Promoter-recognition, biochemical, and physiological effects of these isoforms highly differ. Genes regulated by PR-B are higher in number in comparison to those regulated by the PR-A.

Transfection studies showed that PR-A acts as an inhibitor of the transcriptional activity of PR-B, yet some authors proposed that this would not be relevant in real physiology, since this effect occurs when PR-A is in high excess [102]. PR gene polymorphisms linked to breast and reproductive cancers appear to increase PR-B isoform, rather than affecting transcriptional activity [55]. PRs act as ligand-activated transcription factors on promoters containing progesterone response elements (PREs) such as c-myc or initiate kinase cascades (c-Src, MAPK) to activate other transcription factors such as the ETS family [32]. The nonreceptor tyrosine kinase Src is a central player in mediating fast activation of signaling cascades by all steroid receptors (SRs) [88]. The steroid receptor coactivator (Src) family consists of three members: Src-1, Src-2, and Src-3, which exert intrinsic histone acetyltransferase (HAT) activity and modify chromatine [58]. Src is expressed in the normal brain: a small cohort of normal brain samples demonstrated consistent expression of Src-1 and Src-2, but Src-3 was absent in all samples [102].

Progestins are safe and efficient medicines in treatment of endometrium cancer (EC), yet conflicting evidence exists in regard to assess the expression of single PR isoforms or their ratio as predictors of EC prognosis and response to endocrine therapy [104]. Nonetheless, it is more clear that the loss either one or both of these isoforms is associated with higher clinical grade [104]. In vitro studies on human EC cell lines demonstrated that the PI3K/AKT pathway and cell cycle regulatory proteins required for cell proliferation and apoptosis are likely a result of PR-B activity [104]. Some clinical studies indicated that PR-B/PR-A + PR-B ratio was all significantly higher in EC cases responding MPA treatment than in those not responding [114]. Simplistic views may not explain many phenomena of progesterone signaling. It should be kept in mind that vast number of factors may determine the net outcome of progesterone on tumor growth including examined species (mouse, rat, human), applied doses, diverse post-translational modifications and interactions with many co-repressor, and coactivator proteins. Plausibly, stimulation of proliferation versus cell differentiation by progesterone via both PR-A and PR-B is not separated by sharp lines, and therefore, presence of both PRs is correlated with lesser tumor aggressiveness. On the other hand, reviewing a number of publications raises a general opinion that the shift from proliferative to inhibitory effects of progesterone associates with increasing concentrations.

Understanding the dual effects of progestins on cell proliferation: clues from breast cancer

The actions of progesterone on proliferation of both benign and malignant breast epithelia are far from being simple. Progesterone effects were analyzed in normal human breast tissues xenografted into athymic mice [24]. In untreated breast xenografts, the PR was almost undetectable and proliferation was at basal levels and peculiarly, progesterone alone did not trigger cell proliferation [24]. The estradiol threshold necessary to induce PR expression in human breast epithelial cells was lower than that required to induce proliferation and a

majority of proliferating breast cells did not express PR [24]. Hence, higher incidence of breast cancers in progestin-added HRT in comparison to single estrogens can not be solely attributed to progesterone carcinogenicity. Continuing presence of progesterone simultaneous with sustained high levels of estrogens—which should be lesser in normal postmenopausal physiology—may provide "a double hormone-hit" to trigger carcinogenesis.

PR-A isoform acts dominant in progesterone-deficient conditions, which associates with an aggressive phenotype. BRCA1 mutation-carrying transgenic mice exhibits an increased relative abundance of PR-A to PR-B [88]. Nonetheless, in human breast tumor cell lines, PR-B is a stronger transcriptional inducer than PR-A and the proliferative actions of progesterone in breast cancer cells are mediated mainly by PR-B isoform [88]. This dichotomy can again be explained by dual roles of progesterone. Treatment of human breast epithelial cells in 3D culture with progesterone induces cell proliferation but also their differentiation into luminal epithelia and myoepithelial cells [88]. These observations are parallel to epidemiological observations indicating that breast cancers induced by progesterone-containing HRT have a more favorable prognosis. Moreover, ER+/PR+ tumors respond to endocrine therapies better than ER+/PR− tumors in both pre- and post-menopausal women and loss of PR in ER+ tumors associates with a more aggressive phenotype and decreased survival [88].

When breast cancer cells (T47D-YB) that constitutively synthesize PR-B are treated with progesterone, they are accelarated at the first mitotic cell cycle, but thereafter, arrested in late G1 of the second cycle [50]. Continuous progestin exposure, from either multiple sequential treatments with natural progesterone, or from treatment with high doses of synthetic progestins, produced permanent inhibition via high levels of cell cycle inhibitors, p21 and p27 [74]. Based on this biphasic response to a pulse of progesterone, it was suggested that transient or intermittent doses of progesterone stimulate cell growth, while sustained exposure to high-dose progesterone is growth inhibitory [74].

Indeed, epidemiological data reveals that breast gland maturation during first pregnancy will assure a window of hormonal prevention [72]. Gestational hormones will decrease further genomic damage induced by carcinogens or endocrine disrupters by enhancing breast gland differentiation. Moreover, full-term pregnancy offers the maximum physiological protection from breast carcinogenesis, whereas the interruption of pregnancy reduces the protective effect [51]. Progesterone's diverging effects on cell growth may also be caused by splicing variants of the PR. These variants may change the progestin responsiveness of a tissue and involve in the abnormal growth associated with breast cancer [29].

Furthermore, progesterone and synthetic progestins also exert differential effects on gene expression. Progesterone effects are provided by the progesterone receptor (PR) alone, but MPA binds to the progesterone, glucocorticoid (GR), and androgen receptors (AR). Similar to progesterone, MPA at the same concentration and same exposure interval also triggers both proliferative and antiproliferative gene expression in breast cancer cells [94]. MPA induces S100P and AQP3, described in different cancers and which expressions were associated with drug resistance, metastasis, and poor outcome. On the other hand, MPA downregulates oncogenic c-myb and pro-angiogenic KDR/VEGFR2, while progesterone has no influence on the expression of these genes in MCF-7 cells [94].

Further aspects to understand progesterone's dual actions on gliomas: MPA as an anticancer agent at high doses with differential effects on meningioma growth

Initially, estrogen-based HRT consisted only of conjugated equine estrogens unopposed by progesterone, which prominently increased the incidence of endometrial cancer [122]. The addition of a progestin to HRT prevented endometrial cancer via providing cell differentiation. Kelley and Baker (1961) were the first to report an objective response in patients with advanced endometrial cancer treated with various progestins [122]. In endometrial and renal carcinoma, doses of 400 to 1000 mg of MPA i.m. per week are recommended initially (MPA Product Data Sheet). In breast cancer, the recommended dosage is 500 mg/day intramuscularly for 28 days. The woman should then be treated with a maintenance schedule consisting of 500 mg twice weekly until progression (MPA Product Data Sheet). If an accelerated disease progression is witnessed at any time, MPA treatment should be stopped. The dose of progestin may be important for determining the antineoplastic efficacy of these agents: high doses of drugs could significantly enhance the response rate and even prolong survival [38].

In pre-menopausal patients, high-dose MPA (HD-MPA) exerted antitumor activity at least equivalent to oophorectomy. The Adjuvant Breast Cancer Project Belgium started a multicentric randomized trial aiming at assessing the efficacy of adjuvant therapy with HD-MPA intramuscularly (i.m.) administered in women who underwent to surgery for early breast cancer [38]. Axillary node-positive (NP) patients were also given CMF chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil). Hematological and systemic tolerances to CMF were better in the HD-MPA group [38]. Due to a myeloprotective effect of HD-MPA, the patients underwent less delay and/or dose reductions of chemotherapy and could be treated with higher doses of CMF therapy [38].

Five hundred forty-one patients were randomized: 260 patients in the node-negative (NN) group and 281 patients in the NP group among whom respectively 246 and 270 were fully evaluable. The relapse-free survival was significantly improved in the NN group treated with HD-MPA [38]. Contrary to what was witnessed in NN patients, relapse or death rates did not differ for the whole group of NP patients. However, when patients were grouped in regard to their ages (< 50; > 50 years), differences appeared. Patients under 50 years had a worse prognosis when treated with combination of CMF and HD-MPA [38]. On the contrary, patients over 50 years who were treated with CMF and HD-MPA had a significantly longer relapse-free interval (+ 25%) in comparison to those treated with single CMF protocol [38].

These results are of quite interest in planning HD-MPA therapy protocols in treatment of far advanced cancers and GBM. MPA is a partially androgenic progestin and stimulates antiapoptotic effects in pre-menopausal women's tumor tissues in the copresence of high levels of other female sex hormones. On the other hand, MPA may increase chemotherapy efficacy in post-menopausal women with predominant progestin (or antiprogestin via receptor downregulation?—as will be discussed below) effects. The capability of MPA to enhance chemotherapy tolerability is important and may also be relevant in suppressing myelotoxicity of brain tumor-specific agents (temozolomide, lomustine) and may provide that intense doses of chemotherapy could be applied. Studies on MPA effects on human meningioma growth also provide clues to understand dual actions of progestins on glioma. A sex hormone dependence is most obvious in meningiomas for the following reasons: (a) meningiomas are more common in women than in men (2:1 and 4:1 female/male ratio for intracranial and spinal meningiomas, respectively); (b) the course of growth is more rapid during periods of hormonal modification such as the end of the menstrual cycle or during pregnancy; (c) the incidence of meningiomas is higher in individuals with other hormone-modulated tumors such as cancers of the breast, ovary, and endometrium; and (d) remarkably high titers of high-affinity/limited-capacity PR are present in over 70% of meningioma cytosols [80].

Hensiek et al. represented a case of regression of a cerebral metastasis of a renal cancer with a subsequent development of meningioma after nephrectomy and under treatment with continuous MPA [57]. Vadivelu et al. presented a patient under long treatment with a progestin, megestrol acetate, who developed multiple intracranial meningiomas [115]. Cessation of megestrol treatment led to shrinkage of multiple tumors and to the complete vanishing of one tumor. But interestingly, treatment of five meningioma patients with HD-MPA (1000 mg, i.m. once weekly for 17 to 29 weeks) neither induced nor reduced growth of their tumors [66].

A series of studies have shown that HD- MPA is capable to reduce growth fraction of human meningiomas both in cell culture and in clinical conditions [79, 80, 118]. In untreated meningioma specimens, mean PR values were 54.9 fmol/mg protein (range 0–586) and 2813 fmol/g tumor (range 0–17,168), respectively. On the other hand, in MPA-treated patients, average PR levels were 15.6 fmol/mg protein (range 0–69) and 338.3 fmol/g tumor (range 0–1190), respectively [80]. Moreover, in subjects of two-stage resection of meningiomas, MPA significantly lowered PR levels in meningioma cells. Overall, clinical cases and experimental studies showed that despite MPA and progestins may accelerate growth of meningiomas, much intense doses of MPA may be capable to reduce growth fraction of meningiomas in association with reduction of PRs. Again, these results strengthen our hypothesis that high doses of progestins could cause tumor regression via PR downregulation.

Progesterone levels and metabolism in glial tumors

Benign brain tissue can convert pregnenolone to progesterone and progesterone can be further metabolized to several A-ring reduced compounds [119]. By studying four astrocytic tumors, it was found that only one low-grade (II) cerebellar astrocytoma is capable to convert pregnenolone to progesterone. But among three other cerebral astrocytomas (grades I, III, and IV respectively), none had such activity [119]. On the other hand, Melcangi et al. have found that rat (C6) and human (1321N1) glioma cells are capable to convert progesterone to 5α-reduced metabolite dihydro-progesterone (DHP) and DHP to 3α-hydroxylated form tetrahydro-progesterone (THP) [82]. Median progesterone levels in brain tumor tissue are 0.36 pg/mg, whereas concentrations ranging from 5 to 10 pg/mg were found in normal brain [117]. A negative correlation was found between serum beta-lipoprotein levels and a malignant brain tumor in women above 50 years by studying 75,050 persons from Mid-Swedish geographical districts [41]. Beta-lipoprotein is an approximate measure of LDL, which participates in steroid-precursor cholesterol supply to the CNS; and progesterone derivatives are the only sex steroids synthesized in the CNS [41]. Thus, it would not be illogical to assume that intracerebral progesterone levels do negatively correlate with malignant brain tumors at least in women [41].

Progesterone receptor expression in gliomas: opposite findings obtained with affinity-based assays versus immunohistochemical and PCR analyses

First in 1983, Poisson demonstrated progesterone-binding via dextran-coated charcoal (DCC) assay in two of nine glial brain tumors (150 and 170 fmol/g tissue, respectively) [93]. Concolino et al. studied two astrocytomas and one oligodendroglioma for the presence of PR via DCC assay and they detected PR activity only in cellular nuclei of the oligodendroglioma [28]. Considering very low levels such

as 5 fmol/mg protein as positive, Sica et al. suggested that 62.5% of all malignant neuroepithelial tumors of the brain are PR-positive [106]. At the time of this publication (1989), the term "malignant neuroepithelial tumor" was used according to the International Classification of Nervous System Tumors published by Zuelch in 1979, which comprises mainly from malignant glial tumors [106]. Riva et al. assayed PR via DCC and found 3.5% positivity among the 57 samples tested and there was no difference between male and female samples [98]. Paoletti et al. assayed dexamethasone responses in glucocorticoid receptor (GR) positive and negative glial tumor samples [90]. In GR positive samples, dexamethasone doses between 0.016 and 2 μM induced cell proliferation, whereas in GR negative samples, same dexamethasone doses did not cause cell growth [90]. Interestingly, higher doses of dexamethasone strongly suppressed cell proliferation of glioma cells [90]. This is similar to what we witness in U87 and U251 glioma cells with MPA (unpublished observations). Georgakulias reported their assay of 15 gliomas with DCC; they reported 30% of patients with malignant gliomas had PR levels above 10 fmoles/mg protein [42]. Magrassi et al. analyzed PR levels first time via PCR in 12 samples: nine samples were anaplastic astrocytoma, three were glioblastoma. None of the anaplastic astrocytoma samples were positive, whereas all glioblastoma gave positive signals [78]. In 1995, Carroll et al. has published results of PCR surveillance of 28 astrocytomas for PR expression. Sixty-two percent of glioblastomas, 37% of anaplastic astrocytomas, and 25% of the low-grade astrocytomas expressed PR mRNA. These results showed that PR expression occurs more frequently in high-grade tumors than in low-grade tumors [22].

Khalid et al. published results of an IHC (immunohistochemical) analysis of PR in glial brain tumors [69]. GBMs had a significantly higher percentage of PR-positive cells compared with anaplastic ($p < 0.0008$) and low-grade ($p < 0.0001$) astrocytomas [69]. In addition to the tumor cells, cells of microvascular endothelial proliferation and the smooth muscle of tumor vessel walls were frequently PR positive. PR-positive astrocytic tumors had higher Ki-67-LI than PR-negative tumors. Moreover, microvascular endothelial proliferations were strongly positive for PR.

Assimakopoulou et al. published an IHC survey of 90 supratentorial astrocytic tumors [9]. Strong PR nuclear IHC positivity was observed in 27 of 46 (59%) glioblastomas, in nine of 20 (45%) anaplastic astrocytomas, and in two of 24 (8%) astrocytomas. Normal astrocytes remained consistently negative for both sex steroid receptors and PS2 [9]. In many cases, endothelial cell nuclei of apparently normal tumor vessels as well as from vessels with endothelial proliferation expressed PR, whereas no such staining was observed in controls [9].

González-Agüero et al. reported PR isoform expression patterns in astrocytomas [47]. PR expression was observed at mRNA and at protein levels in 66 and 83% of astrocytomas grade III, respectively, whereas 100% of astrocytomas grade IV expressed PR [47]. Almost all PR mRNA content in astrocytomas grades III and IV corresponded to PR-B [47]. Inoue et al. has published production and actions of progesterone in neurogenic tumors [65]. PR isoforms were detected in neurogenic tumors. PR-A and PR-B were equally expressed in meningiomas, but PR-B was the predominant isoform compared with PR-A in astrocytic tumors and schwannomas [65]. There was a statistically significant inverse correlation between PR-A and the proliferation index in meningiomas and astrocytic tumors [65]. They proposed that progesterone involves in development of glial tumors via PR, especially in the inhibition of tumor cell proliferation via PR-A and stimulation of tumor cell proliferation via PR-B [65].

Why did the early DCC-affinity-based studies versus late IHC- and PCR-based studies give opposite results in regard to PR expression? We assume that glial tumor-specific polymorphisms and splicing variants of PR create receptors with low affinity to progesterone leading the situation that the affinity-based studies did not detect PR in glial tumors in early studies. As mentioned above, progesterone levels in glial tumor tissue is also lower than the normal brain [117]. Under these circumstances, the proliferative actions of PR-B isoform may dominate and progesterone may act as a proliferative hormone and as a risk factor for the growth of gliomas. We propose a three-step mechanism in regard to progesterone involvement in glioma growth. (1) Proliferation is induced with the presence of low affinity PRs, low-dose progestins, and under the dominance of the PR-B isoform. (2) Both cell proliferation and differentiation is induced in the presence of intermediate to high doses of progestins via downregulation of PR-B; simultaneously PR-A or other low-affinity PRs begin to be saturated. (3) In the presence of high to intense doses of progesterone and with prolonged exposure, cell differentiation and subsequent cell death events dominantly occur. Now, we will explain these diverging effects of progesterone/PR actions on gliomas.

Progesterone stimulation of glial tumor growth at low doses

González-Agüero et al. studied the effects of progesterone and RU486, on cell growth of two human astrocytoma cell lines with different evolution grades (U373, grade III; and D54, grade IV) [46]. Progesterone (10 nM) significantly increased the number of D54 cells from the second day of culture, and the number of U373 cells on days 3–5. Mifepristone (10 μM) blocked progesterone effects in both astrocytoma cell lines. Progesterone increased S phase of cell cycle in U373 cells (61%, on day 5) [46]. Mifepristone blocked the effects of progesterone on the cell cycle but did not significantly change cell cycle profile when administered alone [46]. PR isoforms

were detected in both cell lines. They suggested that progesterone induces cell growth of human astrocytoma cell lines through the interaction with its nuclear receptor [46]. Cabrera-Muñoz et al. have published regulation of PR isoform content in human astrocytoma cell lines [20]. They studied the effects of estradiol, progesterone, and their receptor antagonists (ICI 182,780 and mifepristone) on PR isoform content in U373 and D54 human astrocytoma cell lines derived from grades III and IV astrocytomas. In U373 cells, they also evaluated the effects of PR-A overexpression on cell growth [20]. They observed that in U373 cells, estradiol increased the content of both PR isoforms, whereas in D54 cells, it had no effects. Estradiol effects were blocked by ICI 182,780. In both cell lines, PR isoform content was downregulated by progesterone after estradiol treatment. This effect was blocked by mifepristone. They observed that overexpression of PR-A significantly diminished the increase in U373 cell number produced after PR treatment [20]. They suggested a differential PR isoform regulation depending on the evolution grade of human astrocytoma cells, and an inhibitory role of PR-A on progesterone effects on astrocytoma cell growth [20].

Hernández-Hernández OT et al. have studied progesterone and estradiol effects on SRC-1 and SRC-3 expression in human astrocytoma cell lines [59]. In U373 cells, progesterone did not modify SRC-1 expression, but in D54 cells, it increased SRC-1 protein content after 24 h, but reduced it after 48 h [59]. Estradiol did not change SRC-1 expression in any cell line. SRC-3 expression was not regulated by either estradiol or progesterone [59]. Progesterone (10 nM) also induced synthesis of Cyclin D1, VEGF, and EGFR in human glioma cells and Src-1 involves in induction of VEGF [58].

Progesterone (10 and 100 nM) also induces PIBF (progesterone induced blocking factor) mRNA expression in U373 GBM cells, which lasted 24 h and which is inhibited by mifepristone [48]. PIBF protein was localized in both the cytoplasm and nucleus and was released into the extracellular medium. PIBF (200 ng/mL) significantly increased the number of U373 cells on days 2–5 via associating with IL-4 receptor, and increasing JAK1 and STAT6 phosphorylation [48]. In scratch-wound and transwell assays, progesterone (10 nM) enhanced the number of D54 and U251 cells migrating from 3 to 48 h, which was blocked by mifepristone and an oligonucleotide antisense against PR [91]. Progesterone (10 nM) activated cofilin, a protein essential in the actin remodeling during cell motility since it induces the formation of free barbed ends and involves in tumor invasion [91]. Interestingly, mifepristone alone and with progesterone also induced cofilin activation at early periods of treatment, but decreased this activation at later periods.

Hlavaty et al. have shown that U87 and LN-229 human GBM spheroids lacked nuclear PR expression, but expressed membrane PRs, PGRMC1. and PAQPR7; and they also revealed that low dose (10 ng/ml) of progesterone stimulated, while higher dose (30 ng/ml) inhibited growth fraction in these spheroid cultures [61]. They have also observed that progesterone also stimulated protein levels of the membrane PRs, PGRMC1, and PAQPR7; but this stimulation was lesser at higher (30 ng/ml) dose of progesterone than its lower (10 ng/ml) dose [61]. The publication did not mention whether the Ki67 index/growth fraction of the spheroids and the protein levels of membrane PRs were measured after the same progesterone-treatment periods. Here, we speculate that lowering of Ki67 index with higher dose of progesterone may also coincide with the downregulation of membrane PRs.

Plunkett et al. implanted nude rats with U87MG GBM cells intracranially [92]. In their initial study, survival was compared in males and females. The second-phase study groups included (1) males, (2) females, (3) ovariectomized females, (4) sham ovariectomized females, (5) ovariectomized rats given estradiol benzoate for 21 days, and (6) ovariectomized rats given progesterone for 21 days. Female nude rats survived longer than male rats implanted with U87MG cells [92]. In the second phase, ovariectomized, male, and progesterone-treated rats died at approximately 19 days, whereas the female, sham-treated, and estrogen-treated animals died 23 to 25 days after tumor cell implantation. The authors proposed that female nude rats implanted with human GBM cells have a survival advantage over male rats and that estrogen provides the advantage [92].

In 2014, German-Castelan et al. studied the effects of progesterone and mifepristone on growth and infiltration of U373 cells derived from a human astrocytoma grade III, implanted in the motor cortex of adult male rats, using two treatment schemes [44]. In the first one, 15 days after cell implantation, rats were daily subcutaneously treated with vehicle, progesterone (1 mg, since rats weigh around 250 to 300 g, this dosage approximately corresponds to 3.3 to 4 mg/kg), mifepristone (5 mg), or progesterone + mifepristone (1 and 5 mg, respectively) for 21 days [44]. In the second one, treatments started 8 weeks after cell implantation and lasted for 14 days. In both schemes, they found that progesterone significantly increased the tumor area as compared with the rest of the treatments, whereas mifepristone blocked progesterone effects. Lastly, in 2016, Germán-Castelán et al. investigated the effects of progesterone on the growth and infiltration of U87 GBM xenografts implanted into the cerebral cortex of male rats and the involvement of nuclear PRs in these effects [43]. Eight weeks after the implantation of U87 cells in the cerebral cortex, they administered antisense oligodeoxynucleotides (ODNs) to silence the expression of PR, which lasted 15 days and was administered at the site of GBM implantation. Vehicle or progesterone (4 mg/kg) was subcutaneously injected for 14 days starting

1 day after the beginning of ODN administration. They observed that progesterone significantly increased glioblastoma tumor area and infiltration length, whereas PR-antisense ODNs blocked these effects [43].

Progesterone inhibition of neuroblastoma and glioblastoma growth at high doses

Atif et al. revealed that high concentrations of progesterone (20, 40, and 80 μM) acted neuroprotective in primary cortical neurons but exerted significant cytotoxicity in a tumor cell line, PC-12 (pheochromocytoma) [10]. At high levels, progesterone significantly ($p < 0.05$) decreased SK-N-AS cell vitality in vitro, and this effect was not blocked either by 5α-reductase antagonist finasteride or the PR antagonist mifepristone. On the other hand, even at very high levels, progesterone did not influence viability of primary cortical neurons or human fibroblasts. In nude mice, progesterone (50 and 100 mg/kg) reduced neuroblastoma growth by ~ 50% over 8 days of treatment [10]. No progesterone toxicity was witnessed in the mice, as measured by body weight and activity. The bioavailability of progesterone 24 h after the last injection in the serum of treated animals was high (10–33 μg/mL corresponding to 31.9–105.1 μM) [10]. Progesterone lowered levels of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP-9, MMP-2), which play important roles in tumor angiogenesis [10]. High-dose progesterone blocked tumor growth via apoptosis and lowering cell proliferation, as revealed by higher levels of cleaved caspase-3 and decrease in the proliferating cell nuclear antigen (PCNA). Progesterone induced a significant increase in PR-A expression of ~ 82 and 93% at 50 and 100 mg/kg doses, respectively. They observed ~ 26 and 21% decreases in PR-B expression with 50 and 100 mg/kg doses of progesterone, respectively [10].

Atif et al. then assessed the anticancer effects of progesterone against the growth of grade IV human U87MG and U118MG (PTEN mutant, p53 wild type), U87dEGFR (EGFRvIII mutant), and LN-229 (PTEN wild type, p53 mutant) cells in vitro, and in a subcutaneous xenograft (U87MG) mouse model of GBM [12]. They revealed significant ($p < 0.001$) cell kill in U87MG, U87dEGFR, and U118MG cells after 3 days of progesterone treatment at high concentrations (10, 20, 40, and 80 μM), whereas lower concentrations of progesterone (0.1, 1, and 5 μM) were not cytotoxic [12]. After 6 days of treatment, this cell-kill effect was more pronounced and at lower concentrations (0.1, 1, and 5 μM), they revealed a significant cell proliferation effect of progesterone during 6 days of exposure in all GBM cell lines [12]. To determine whether progesterone-induced cell kill in U87MG, U87dEGFR, and U118MG cells is PR-dependent, they evaluated the effect of the PR antagonist mifepristone in combination with progesterone on the viability of those cell lines [12].

All the cell lines showed a significantly enhanced proliferation following repeated exposures to progesterone alone at low concentrations (0.1, 1, and 5 μM) for 6 days which was blocked with mifepristone at low concentrations [12]. In opposite, mifepristone did not inhibit the cell kill-inducing effects of high concentrations of progesterone at 3 and 6 days in any tested cell line and even, mifepristone showed a progesterone mimetic effect at high concentrations and augmented tumoricidal activity of high-dose progesterone [12]. Progesterone at high concentrations (40 and 80 μM) significantly ($p < 0.05$) induced p53expression in U87MG, U87dEGFR, andU118MG cells but not in LN-229 cells [12]. Tumor-bearing mice were treated daily with high progesterone doses of 100 or 200 mg/kg or vehicle; and after 5 weeks of progesterone treatment, they observed 73.61 and 60.65% inhibition of tumor growth ($p < 0.001$) at 100 and 200 mg doses, respectively [12]. Furthermore, progesterone treatment significantly ($p < 0.001$) enhanced the survival of tumor-bearing mice by 60%. Progesterone treatment—even at this very high dosage—did not induce toxicity and control mice receiving only progesterone (100 or 200 mg/kg) did not exert any toxic effects either. A significant ($p < 0.05$) decline in the expression of tumor vascularization markers CD31, VEGF, and MMP-9 occured in both progesterone-treated groups [12]. Progesterone at both doses inhibited PI3K/Akt/mTOR signaling as evidenced by a significant ($p < 0.05$) decrease in the expression of phospho-Akt and mTOR [12]. The authors suggested that progesterone acts through genomic effects at low concentrations, and through nongenomic effects at high concentrations [12].

Atif et al. then analyzed the combined effects of progesterone and temozolomide (TMZ), to test whether progesterone enhances the antitumor effects of TMZ and reduces its side effects [11]. Two WHO grade IV human GBM cells lines (U87MG and U118MG) and primary human dermal fibroblasts (HDFs) were repeatedly treated with progesterone and TMZ either alone or in combination for 3 and 6 days. Progesterone and TMZ individually induced tumor cell death in a dose-dependent manner and progesterone at high doses (~ 80 μM) produced more cell death than TMZ alone. In combination, progesterone increased the cell kill-inducing effect of TMZ (100 μM) in glioma cells. In human dermal fibroblasts, progesterone did not reduce viability even at the same high cytotoxic doses, but TMZ did so in a dose-dependent manner [11]. Furthermore, progesterone reduced TMZ toxicity in human dermal fibroblasts. Progesterone alone and in combination with TMZ inhibited the EGFR/PI3K/Akt/mTOR signaling pathway and MGMT expression in U87MG cells, thus blocking cell proliferation

and chemo-resistance. Moreover, progesterone and TMZ blocked cell migration in U87MG cells both alone and in synergy [11].

Clues that high doses of MPA and mifepristone (partial PR-antagonist/agonist) may act via similar pathways

High doses of MPA downregulates PR-B in endometrial cancer

Classen et al. showed that MPA (1 μM) suppressed growth of hormone-dependent human breast cancer cells, yet decreased the cellular ER content by 27% and the PR content by more than 80% [25]. Van Den Berg et al. showed that MPA could downregulate PR expression also via heterospecific modulation of the GR [116]. In the human uterus cell cultures, native hormone progesterone upregulates stromal PR expression but downregulates epithelial PR expression [112], but MPA downregulates PR expression both in uterine stromal and epithelial cells [2, 26]. GOG study-211 used MPA as a neoadjuvant intervention for women who had been recently diagnosed with endometrial cancer after the initial biopsy [122]. These patients then underwent hysterectomy, and PR levels and downstream effectors were measured [122]. PR levels declined significantly in most patients. Downregulation of PR includes modification of PR expression at the DNA, mRNA, and protein levels [122].

Zaino et al. reported a study conducted on 75 women with endometrial cancer, 59 of whom received MPA for 21–24 days immediately prior to hysterectomy. Thirty-seven tumors (63%) had a partial histologic response and post-treatment specimens showed downregulation of PR and PR-B [123]. As stated above, Atif et al. argued that high doses of progesterone acted via nongenomic progesterone receptors as mifepristone were not capable to block progesterone actions and unexpectedly exerted progesterone-mimetic effects in glioblastoma [12]. But as we will explain below, mifepristone also has PR agonistic functions [83] and mifepristone and progesterone mutually reinforce their antiproliferative and apoptotic actions on endometrial cancer cells at high doses [85, 86]. Therefore, we think that progestins at supraphysiologically high doses and mifepristone act via similar pathways.

Mifepristone has partial PR agonist activity and synergies with MPA in suppression of endometrial cancer growth

Mifepristone induces binding to a progestin-responsive element of homodimers and heterodimers of the humanPR (hPR) isoforms A and B, present inT47-D breast cancer cells or in HeLa cells expressing recombinant proteins [83]. The resulting complexes were indistinguishable from those induced with the progestin promegestone with respect to specificity and affinity [83]. In the presence of mifepristone, the PR-B-mifepristone-TAF-1 (transcription activation function complex) activated transcription from a reporter gene containing a single progestin-responsive element [83]. In contrast to PR-B, PR-A was not able to activate transcription in the presence of mifepristone [83].

Tung et al. have shown that mifepristone stimulates gene transcription via binding to PR-B; moreover, when both PR-A and PR-B are copresent, PR-A becomes dominant in the presence of mifepristone [113]. We think that oversaturation of PR-B, its subsequent downregulation, and activation of PR-A occurs in the presence of mifepristone, which may occur similarly in the presence of high levels of progestins. Indeed, high concentrations of progesterone (32 to 95 μM) and mifepristone (23 to 70 μM) augmented the effect of each other, reducing the endometrial cancer (Ishikawa) cell proliferation in vitro via cell cycle arrest and apoptosis [86]. We propose that both agents at high doses acted agonistic on PRs at early periods of treatment but then acted synergistically antagonistic via receptor downregulation.

Could we achieve serum concentrations of progestins in humans which are used in cell culture? Or do we need such concentrations?

In nude mice, progesterone (50 and 100 mg/kg) inhibited neuroblastoma growth by ~ 50% over 8 days of treatment [10]. The bioavailability of progesterone 24 h after the last injection in the serum of treated animals was significantly increased (10–33 μg/ml corresponding to 31.85–105.1 μM) [10]. In human breast cancer, high-dose MPA treatment (1500 mg/day per os) yields peak concentrations between 1.5 and 6 μg/ml [70]. Placental concentrations of progesterone are between 5 and 20 μg/ml corresponding to 15.9–63.7 μM [81]; thus, it can be concluded that antitumor concentrations of progesterone are achievable. Likely due to the fact that progesterone levels reach up to 160 μM at late gestational phases, synthetic progestins also exert very low toxicity such that even intravenous and intraperitoneal LD50 doses of MPA is 400 mg/kg in rats, respectively, which corresponds to a 18.67-fold greater dose of MPA applied for breast cancer treatment in humans (MPA Product Data Sheet). Progestins are lipophilic hormones and cross the blood-brain barrier, and in humans, a transfer from plasma to cerebrospinal fluid occurs of about 10% for progesterone. In female rats, we observed that 20 mg/kg of MPA (corresponding to an approximate 1.4 g/day) reduced tumor volumes by 50% (unpublished data). It is also likely that lower systemic concentrations of progestins may be sufficient in vivo to suppress glioma growth either via accumulating selectively in tumor tissues and/or changing tumor-microenviroment. An alternative approach would be continuous infusing progesterone analogues directly

into the tumor cavity via Ommaya reservoirs since they are much less toxic than cytotoxic chemotherapy.

A proposal to utilize ulipristal against high-grade glial tumors

Mifepristone is a likely candidate in glial tumor treatment, yet there exist clinical problems in applying mifepristone, in 15% of the cases, mifepristone can cause prolonged uterine bleeding [30]. Adrenal insufficiency or nausea [101] and pelvic infections [108] may also occur with mifepristone treatment. Ulipristal (Fig. 5) is a selective PR modulator (SPRM) used in contraception and in treatment of uterine fibroids which is more effective than mifepristone as a post-coital antifertility drug [97]. In normally cycling women, ulipristal has no major effects on menstrual cyclicity [111]. In treatment for menometrorrhagia during the pre-menopause, SPRMs induce amenorrhea while maintaining endogenous estrogen secretion [19]. Moreover, in treatment of bleeding associated with leiomyomas, both mifepristone and ulipristal reduce bleeding, yet mifepristone induces more frequent endometrial hyperplasia, which is a risk factor for endometrial malignancy. Ulipristal exerts lesser antiglucocorticoid activity in comparison to mifepristone [60]. Moreover, at higher dosages, mifepristone, but not ulipristal, exert also glucocorticoid activity [13], which may be detrimental for the immune system. Yet, it shall be also admitted that ulipristal is not devoid of side effects and its adverse effects in trials included headache, breast tenderness, nausea, and abdominal pain [109]. Hence, risks and benefits of ulipristal treatment shall also be carefully considered.

Ulipristal has superior antiproliferative efficacy than mifeprisone in spheroid cultures of T47D human breast cancer cells [75]. In ovarian cancer cells, ulipristal at a dosage of 40 μM induces growth arrest by triggering accumulation of Cdk inhibitors p21cip1 and p27kip1and also induces cell death following cell cycle arrest [49]. Moreover, cisplatin- and paclitaxel-resistant ovarian cancer cells do not develop resistance against ulipristal, even in IGROV-1 carcinoma cell line, IC_{50} of ulipristal is lower in paclitaxel-cisplatin resistant subline [40]. Moreover, in steroid-free medium, a much lower dose of ulipristal (1 μM) was capable to reduce growth of

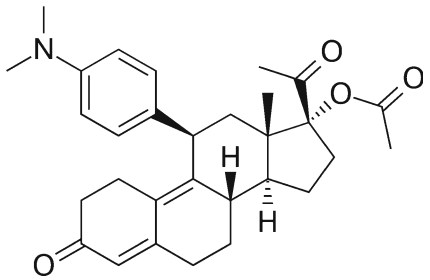

Fig. 5 Ulipristal

MDA-MB-231 human breast cancer cells both in the absence and presence of progesterone and reduces levels of the antiapoptotic bcl2-L_1 protein [36]. Lastly, in BRCA1-mutant breast tissues implanted into nude mice, PR-B expression is lost and progesterone induces proliferation, which can be overcome with ulipristal [27] indicating that ulipristal may be efficient in cancers with defective DNA repair.

Immunity and progesterone: from pregnancy-associated immune modifications to immune anticancer activity

As suggested above, pregnant women undergo intense modifications in their immune system to prevent rejection of the fetus, which acts like a semiallogeneic graft due to paternal antigens. It is well established that certain immunosuppressive pathways are activated to prevent fetal rejection. On the other hand, such immunosuppressive actions are unique and not resembling to the artificial and dangerous inhibition of immunity, which we employ to suppress rejection of solid organ transplants (e.g., cyclosporine). The lesser-known feature of pregnancy is that the gestational process is also associated with stimulation of certain immune pathways to protect the mother and the baby against microbial pathogens. It is plausible that similar immunostimulatory mechanisms may associate with pregnancy reduction of risk of malignancies. Indeed, splenocyte cytotoxicity against breast cancer cells is augmented in pregnant rats in comparison to nonpregnant counterparts [23]. Here, we underline mechanisms which mediate pregnancy-associated immune stimulation to strengthen our proposal that high-dose progestins or antiprogestins may act via blocking embryonic mimicry of malignancies.

Type I and/or type II interferons (IFNs) play essential roles to provide uterine receptivity to implantation in mammals [14]. Gene expression effected by IFNs may be augmented, suppressed, or blocked, but the majority of these include IFN-stimulated genes (ISGs). Effects of IFNs are versatile from pregnancy recognition in ruminants by IFN-tau to modifications of the uterus and uterine vasculature [14]. For the most effects of IFNs on the uterus, progesterone is permissive to ISG expression, with genes being triggered by IFN or induced by progesterone and further augmented by IFN [14].

To illuminate protective mechanisms of pregnancy against breast cancer, Misra et al. studied the effects of pregnancy and estrogen + progesterone treatment (at the levels of pregnancy) on the gene expression in mammary gland [84]. The top commonly increased genes include immunoglobulin heavy chain (α-polypeptide) groups, MMP12, TREM2 (triggering receptor expressed on myeloid cells), GP49B, CCL9 (chemokine ligand 9), C/EBP (CCAAT/enhancer-binding protein-α) (C/EBP), MSR2 (macrophage scavenger receptor 2), TNSF13 (tumor necrosis factor-ligand superfamily member 13), immunoreceptor Ly49si3, and MT1a (metallothionein

1a) [84]. MMP12 is a macrophage metalloelastase. TREM2 is an important modifier of inflammatory responses. GP49B belongs to the immunoglobulin superfamily and regulates Tcell priming [84]. CCL9 is an interferon-γ-inducible β-chemokine and exerts prominent anticancer activity through attraction of cytotoxic T lymphocytes and blockage of neovascularization, and is maintained by C/EBP [84]. TNFSF13 is an important regulator of B cell development [84].

Blakely conducted a very similar study and studied pregnancy and estrogen + progesterone-induced changes in mammay gland [18]. Among the 70 differentially expressed genes, a significant portion was immunity genes. Enhanced expression of multiple immunoglobulin heavy and light chain genes indicated an increase of plasma cells, whereas upregulation of *Mmp12* and *Tnfrsf21* was compatible with higher numbers of macrophages and T cells [18]. Similarly, enhanced antibacterial and antiviral activity was indicated by the upregulation of *Lbp*, *Lcn2*, and *Ccl5* [18]. But how would progesterone analogues may affect the antitumor immunity in cancer patients? When considering that both the native progesterone and MPA could also bind glucocorticoid receptors, it can be questioned that these hormones may detrimentally affect the anticancer immunotherapy. There exist few studies on this issue, but the majority of the available data indicates a beneficial rather than a detrimental effect of MPA on the outcome of chemotherapy and immunotherapy. Indeed, MPA lowered the marrow toxicity of chemotherapy in patients with breast, colon, and head and neck cancers without lowering antitumor efficacy [35].

Lissoni et al. performed a clinical trial with or without MPA in patients with metastatic renal cancer in maintenance therapy with IL-2 following response or stable disease (SD), to determine the effect of MPA on free-from progression (FPP) period [76]. Thirty consecutive patients were randomized to single IL-2 treatment (3 million IU twice/day for 5 days/month s.c.) or IL-2 plus MPA (500 mg orally 1 day/week) without interruption until disease progression [76]. A FPP period longer than 1 year was witnessed in 8/14 patients (57%) treated with IL-2 plus MPA and in only 3/16 (18.8%) patients treated with IL-2 alone, which was statistically significant [76]. At the cellular level, Werner et al. demonstrated that the antitumor activity of IFN-α and MPA was not antagonistic, rather synergistic in breast and ovarian cancer cell lines [120]. Witkiewicz analyzed the effect of progestins on immune cells in endometrium cancer [122]. The pre- and post-treatment endometrial specimens of 15 progestin-treated patients with complex atypical hyperplasia or well-differentiated endometrial cancer were evaluated [122]. Ten of 15 patients responded to progestin treatment, and four patients had persistence or progression of the disease [122]. Progestin treatment caused an increase in cytotoxic T cells in areas with decidual reaction [122]. Before treatment, the majority of the granzyme B+ cytotoxic T cells in atypical hyperplasia and endometrial carcinoma were CD8+ T cells, whereas up to 80% of cytotoxic T cells were natural killer cells following progestin treatment [122]. Overall, available data indicates that MPA does not block even stimulates anticancer immunity in clinical conditions.

Questions need to be answered with animal models: the preferred substance, the preferable route of administration, and interactions with antiedema treatment

We conclude that high dose of MPA would be suitable for applying as an endocrine treatment for high-grade glial tumors. Nonetheless, the dose range and efficacy shall be tested in various animal models and especially in tumors implanted intracranially. We do believe that nude mice experiments with subcutaneous implantation of glial tumors are not suitable to answer these questions. The efficacy of progestins shall be tested in three different—yet always intracranial—glioma models including "autochtonous tumors" (such as 9L, C6, etc.), in immunosuppressed mice intracranially implanted with glial tumors and in transgenic mice which spontaneously develop high-grade glial tumors. For the breast cancer treatment in humans, depot forms are given with subcutaneous application of MPA, which are liposoluble and release the hormone for prolonged periods, which may also be preferred for adjuvant applications in glial tumor treatment. As we explained above, ulipristal—even at low doses—may also be effective in treatment of glial tumors via direct antagonism of the progesterone receptor (instead of PR downregulation achieved with high dose of MPA). However, there only exist experimental data suggesting antitumor efficacy of this compound against aggressive breast and ovarian cancers; but hitherto, no study was conducted in regard to ulipristal effects on glial tumors. Both in vitro and in vivo dose-optimization studies are necessary for this compound. Lastly, since high doses of steroids can exert cross reactivity for different subtypes of steroid receptors, one could ask likely interactions of progestin treatment with antiedema therapy employing glucocorticoids (such as dexamethasone). We do not have in vivo data in regard to this concern, yet our in vitro observations (submitted for publication) demonstrated slight antagonistic interactions between these two types of hormones in terms of 3-dimensional glioma invasion, suggesting that these two hormones shall be given in different time periods of treatment. Another question would be how progestins alone would affect peritumoral edema in glial tumors. Our unpublished observations with MR imaging and tumoral sections of rat glioma did not demonstrate any edema-increasing activity of the progesterone analogues alone.

Any surrogate marker for patient selection in regard to endocrine treatment of high-grade gliomas?

We strongly believe that proper patient selection is critical in applying adjuvant endocrine treatments for high-grade glial tumors. In regard to the brain tumors in general, some of recent studies showed lack of efficacy of mifepristone (a PR antagonist) in unresectable meningiomas (Elmaci et al. 2016). However, none of these recent studies applied a patient selection strategy. There exist many anecdotal reports and small case series showing dramatic responses of some meningiomas (especially multiple meningiomas) to mifepristone treatment (Elmaci et al. 2016). In multiple meningiomas, the female to male ratio of incidence is 8 to 1, in comparison to unifocal meningiomas where the female to male ratio is 2 to 1. But unfortunately, none of these studies showed any correlation between PR expression and response to mifepristone treatment (Elmaci et al. 2016). Our working hypothesis is that the relative degree of PR downregulation (especially PR-B) but not the pretreatment PR levels per se correlates with antitumor activity. PR-B may be a marker of response, but since progesterone influences very versatile pathways, markers of single cascades alone may not be sufficient to predict the clinical responses. Although time-consuming, preliminary monolayer and 3-dimensional spheroid cultures of glial tumors may be cloned and tested for progesterone activity at various doses. Such studies were intensively made for cytotoxic treatments in 1980s and early 1990s, but we believe that they may be more guiding to predict responses against hormonal treatments especially if conducted in 3D-spheroid models in vitro.

Conclusions

High-grade glial tumors are very fatal and best treatments with optimal surgery, radiotherapy, and temozolomide chemotherapy only provide survivals around 14 months. Without doubt, efforts to develop new molecules suppressing glioma cell proliferation are important. On the other hand, there exists the possibility of repurposal of the currently approved medicines in management of these grave tumors. Endocrine agents such as progestins and antiprogestins are not cytotoxic, not suppressive on bone marrow, and hence, their therapeutic window is much wider than classical chemotherapeutic drugs. Moreover, due to their lack of general cytotoxicity, they can also be applied via intratumoral route, which may selectively kill glial tumor cells while sparing normal brain tissue. Alternatively and additionally, they can be coapplied with already existing chemotherapeutics, as progestins are shown to reduce chemotherapy myelotoxicity without compromising antitumor efficacy. As suggested above, progestins and other PR-modifiers such as mifepristone may act via similar mechanisms through PR-downregulation and inducing cell differentiation. High doses of mifepristone may be tested in high-grade glioma management, yet prominent antiglucocorticoid activity at moderate doses and pro-glucocorticoid activity at higher dosages may hinder its application at prolonged periods. For the first time, we propose that ulipristal may also be a member of antiglioma endocrine armamentarium. In conclusion, we think that antiprogestins and/or high-dose progestins may strongly deserve to be studied in treatment of high-grade glial tumors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and informed consent This study does not involve any human or animal experiments. Hence, no ethical approval or informed consent forms were needed.

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