GLIOBLASTOMA MULTIFORME: A REVIEW OF THE ROLE OF A3AR SIGNALING IN TUMOR EVOLUTION

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ABSTRACT
Glioblastoma multiforme is a grade IV astrocytoma (WHO), being considered the most common and also the most aggressive. One of the treatment alternatives is the manipulation of adenosine receptors such as A3AR, this manipulation could increase the survival time of these patients. Therefore, the focus of this review is to gather several studies on the ability of the A3AR receptor to regulate cell death, proliferation, immunosuppression and angiogenesis through signaling pathways in GBMs.

GLIOBLASTOMA MULTIFORME: UMA REVISÃO DO PAPEL DA SINALIZAÇÃO A3AR NA EVOLUÇÃO DO TUMOR

RESUMO
O glioblastoma multiforme é um astrocitoma de grau IV (OMS), sendo considerado o mais comum e também o mais agressivo. Uma das alternativas de tratamento é a manipulação de receptores de adenosina como o A3AR, essa manipulação poderia aumentar o tempo de sobrevida desses pacientes. Portanto, o foco dessa revisão é reunir diversos estudos acerca da capacidade do receptor A3AR de regular a morte celular, proliferação, imunossupressão e angiogênese através de vias de sinalização em GBMs.

Palavras-chave: Glioblastoma multiforme; Receptor; Adenosine A3; Glioma; Astrocytoma; Denosine.

INTRODUCTION

Central Nervous System (CNS) tumors are classified according to many criteria, such as microscopy, immunohistochemical analysis and, more recently, molecular and genetic parameters [1]. Gliomas are the most common type of brain tumor, accounting for 32% of all the CNS tumors and 80% of the malignant ones [2]. They are divided into: astrocytomas, oligodendrogliomas and ependymomas [3]. Astrocytomas, in turn, are divided by the World Health Organization into grades I to IV according to the histological characteristics and degree of malignancy [4]. Among them, the most common, and also the most aggressive, is grade IV, glioblastoma multiforme [5].

Glioblastoma multiforme is named after its variety of cell types: bipolar cells, fusiforms, fasciculated, small (undifferentiated) or giants. Another typical characteristic is the vascular proliferation that surrounds the areas of necrosis [4]. According to WHO's 2016 update on the classification of brain tumors, GBM is included in the astrocytic and oligodendroglial tumors

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group and can be divided into three subgroups: IDH-wildtype (primary GBM), IDH-mutant (secondary GBM, as an evolution of lower grade astrocytomas) and NOS (not otherwise specified). Furthermore, GBMs can be divided by their three histological variables: giant cell glioblastoma, epithelioid and gliosarcoma [4,6]. Even though the subgroups present different genetic and molecular pathogenesis [2], cellular events seem to be convergent among them: there is an amplification of the activity of receptor tyrosine kinase genes, an activation of the phosphatidylinositol-3-OH-kinase pathway and the inactivation of the p53 and retinoblastoma tumor suppressor pathways [7]. These effects contribute to the development of the tumor, and many other molecular pathways may be affected by its oncogenesis. Therefore, those should be and are studied as possible therapeutic targets for the disease.

Although the survival of patients with GBM has slightly increased, from 6 to 15 months [8,9], they are not cured with tumor resection, because of their diffuse topography and the variable location of tumor cells in the brain [5]. Due to its high infiltrative power, rapid growth [4], as well as for their diffuse character and the poor results achieved with the more traditional treatments [5], it is extremely relevant to explore this subject.

One GBM cell subpopulation requires special attention due to its capacity of self-renewal, multi-lineage differentiation, high mitosis potential and multidrug resistance: they are called GBM Stem-like Cells (GSCs) [10]. They are one of the main reasons for recurrence of tumor and therapy failure. These cells promote angiogenesis and neovascularization, and are also more resistant to chemotherapy and radiation than other GBM or progenitor cells [10–12]. Once treatment success depends on the cells potential to evade chemotherapy, this cell type may be an important therapeutic target for GBM.

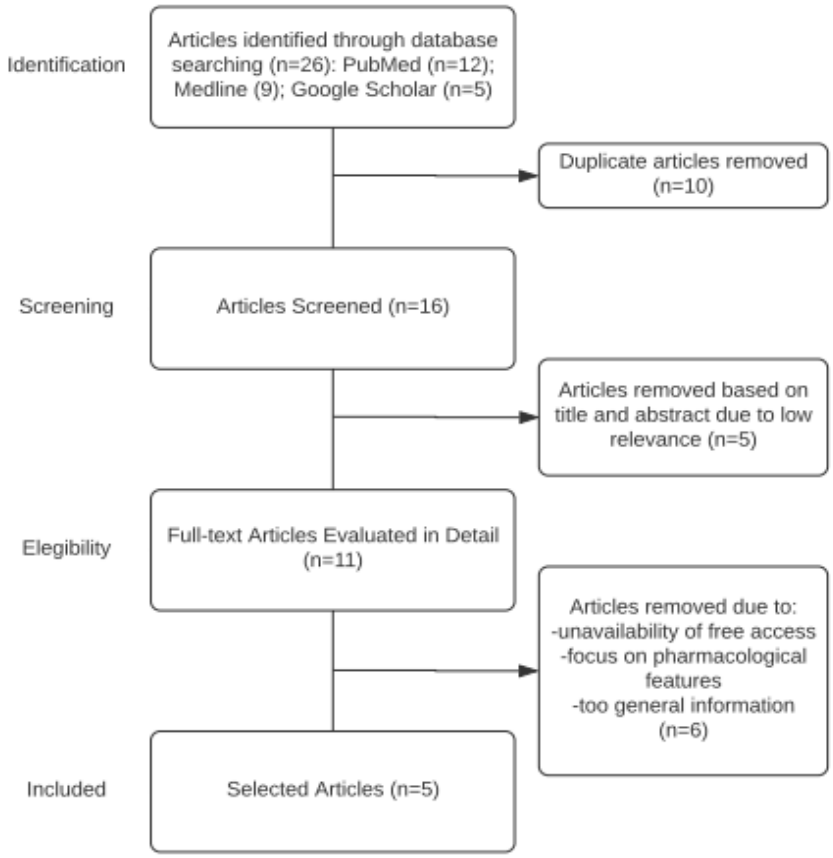
One of the treatment possibilities is the pharmacological manipulation of adenosine receptors, due to their role in tumor growth, especially A3AR [13,14]. Adenosine (Ado) is a purine nucleoside involved in numerous pathophysiological processes, which may vary according to its concentration, target cells, environment conditions and the expression of the receptors [15]. Ado is mainly produced in extracellular matrix by ATP and ADP hydrolysis by CD39 followed by the hydrolysis of AMP by ecto-5'-nucleotidase (CD73) [16–18] . Several molecular events and environmental conditions may induce the production of extracellular adenosine, such as hypoxia or Ado release by metabolically active cells, for instance [19–22]. There are four known cell surface receptors for adenosine, named A1, A2A, A2B and A3, all with different metabolic effects [23]. The

last one, A3AR, was shown to play an important role in the tumorigenesis of GBM, regulating many of its cancerous features [13]. Its impact on GBM is mostly related to the capacity of regulating cell death, proliferation, immunosuppression and angiogenesis through signaling pathways that are the focus of this review.

MATERIALS AND METHODS

In order to get the most recent and reliable information possible on the subject, a systematic review was conducted during the months of May to August, 2020. We used the electronic publicly available databases Medical Literature Analysis and Retrieval System Online (MEDLINE/PUBMED) and Google Scholar, using the key words “glioblastoma multiforme”, “adenosine” and “A3 receptor”, from 2010 to the present.

After gathering all the articles that matched the key words on the databases, the duplicate ones were removed and the remaining passed through a screening process. The inclusion criteria were: focus on the A3AR signaling; use of GBM cells and free full text available online. Two different reviewers realized the process independently, and later compared the selected articles. In case there was not an agreement on the articles obtained, a third reviewer would be consulted, but it was not necessary. Five articles [24–28], thus, were fully analyzed and were the main reference for this review. The flow graph shows the screening process and the table shows the main findings of each article selected.



Author and Reference	Year	Journal	Summarized Outcomes and Findings
S. Gessi et al. [24]	2010	Biochemical Pharmacology	This study demonstrated the role of adenosine on the increased expression of MMP-9 levels in GBM cells. It was shown that the MMP-9 levels are modulated by the A3 adenosine receptor activation and signaling, as well as the ERK 1/2, JNK, Akt and AP-1 pathways. Since MMP-9 levels are related to tumor metastasis, progression and invasion, the A3 adenosine receptor was suggested to be an important target for GBM treatment.
F. Vincenzi et al. [28]	2012	PLoS One	In this study, a few tumor models were used, one of which representing the GBM cells, to demonstrate the impact of Pulsed Electromagnetic Fields (PEMF) on the A3 adenosine receptor activation and further impact on tumor progression. It was shown that the PEMF up-regulates A2A and A3 receptors density and expression, a significant change on the cell response to extracellular adenosine. The author suggested an induction of cell death and apoptosis in tumor cells by the use of PEMF. It was possible to evaluate the intracellular molecular changes after A3AR stimulation using the agonist CI-IB-MECA: decreased cAMP production and [3H]-Thymidyne incorporation, inhibition of NF-kB, increased p53, lactate dehydrogenase and caspase-3 levels. The

			author agreed that there is enough evidence to confirm the dual role of A3ARs signaling in both tumor progression and inhibition, depending on each specific cancer cells characteristics.
A. Torres et al. [27]	2016	Oncotarget	The aim of the study was to understand the impact of the A3AR activation on the chemoresistance phenotype, which is seen in GBM, through the production of multiple resistance-associated protein-1 (MRP-1) in glioblastoma stem-like cells. It was shown a high expression of A3AR on GSCs in comparison to other cells, even other GBM cell lines. The receptor's activation increased MRP1 transporter expression and activity through the PI3K/AKT and MEK/ERK1/2 signaling pathways. A link between purinergic signaling and multidrug resistance (MDR) phenotype was suggested. Therefore, it was concluded that the A3 receptor could be an important pharmacological target for the reversion of the MDR and for chemosensitizing the GSCs.
R. Rocha et al. [26]	2018	International Journal of Molecular Sciences	This study showed the importance of the A3AR on the regulation of the differentiation of GSCs to Endothelial Cells under hypoxia. This feature allows the angiogenesis effect of the tumor and, as a result, its growth and invasivesness. It was shown that the extracellular adenosine concentration and A3AR expression increase under hypoxia, together with higher differentiation rates of GSCs to endothelial cells. It was also demonstrated that the antagonization of A3AR decreased tumor size and blood vessel formation. The authors link this effect to the presence of the hypoxia inducible factor 1-α (HIF-1α), which induces the expression of vascular endothelial growth factor (VEGF); besides, A3AR was said to regulate the expression of endothelial cell markers, such as CD144, CD31 and VEGF itself.
Torres et al. [25]	2019	Cancer Letters	In this study, the aim was to show the promotion of the GSCs' migration through A3AR activation under hypoxia. The hypoxia inducible factors enhance extracellular adenosine production, and this was linked to the higher expression of ectonucleotidases in GSCs under hypoxic conditions. HIF-2 and prostatic acid phosphatase, in particular, enhance the extracellular adenosine production and were associated with the migration and invasion of GSCs. By blocking the A3ARs, it was found that EMT markers, cell adhesion and migration of GSCs decreased under hypoxia. Expression of HIFs, Twist, Snail and N-cadherin increased under hypoxia and a regulation by A3AR was suggested. Besides, A3AR was said to be involved in cell adhesion through the activation of FAK.

RESULTS AND DISCUSSION

The A3 Adenosine Receptors (A3ARs) have been reported to have a dual role in the regulation of cell cycle, either resulting in pro or antiapoptotic effects [23,28]. Even though the A3AR has a lower transcript expression and lower affinity to adenosine than the other receptors [24,26], it was shown that, in GBM, cells exhibit increased levels of extracellular adenosine and A3AR expression than non-tumoral cells. This leads to a higher activity of the receptor, making it an important factor to the development of cancer characteristics [20,24,26–28].

One of A3AR subtypes is a Gi protein coupled receptor (GiPCR) [21], the subunit alpha of the protein negatively regulates the enzyme adenylyl cyclase, leading to a decrease in the levels of cAMP. A2A and A2B ARs are GsPCR, that means they increase the cAMP by the stimulation of adenylate cyclase activity; in GBM cells, this effect is diminished or even inverted, since A3ARs are more expressed and they show the contrary effect [28]. Another A3AR subtype is GqPCR[29,30], whose subunit alpha leads, by the hydrolysis of phosphatidylinositol, to the formation of DAG and IP3, increasing cytosolic calcium levels and activating the protein kinase C (PKC). On the other hand, the beta-gamma subunit of A3ARs stimulates some pathways related with the receptor tyrosine-kinase signaling, such as the PI3K/AKT and the MAPK/ERK1-2/JNK ones [27,31]. These pathways were described to positively modulate the Matrix Metallopeptidase 9 (MMP-9) [24], involved in angiogenesis and invasiveness of the tumor, and also to increase MRP1 transporter expression, involved with the multidrug-resistance phenotype of GBM [27].

First of all, the overexpression of MMP-9 is associated with progression and invasion of several tumors, also being associated with their malignancy [24,32]. The degradation of the extracellular matrix allows cell motility, making metastasis and invasion of tumors possible [25,33]. According to Gessi et al. [24], adenosine modulates metalloproteinase-9 in U87MG glioblastoma cells by activating A3AR. In their experiment, MMP-9 caused an increase in the invasive capacity of U87MG cells. This invasive capacity was decreased when an A3AR antagonist (MRE 3008F20) was used, indicating that A3AR and MMP-9 play a role in modulating the invasive capacity of glioblastoma.

GBM cells produce more MMP-9 than lower-grade tumors and normal brain tissue; besides, it was determined that Ado's higher concentration induces an increase of pro and active MMP-9 levels, which is likely to be associated with the A3AR signaling [24,34]. In order for tumor growth to occur, it is essential for blood vessels to form to supply neoplastic cells with oxygen and

nutrients. Therefore, the use of a selective antagonist to block A3AR seems to be an alternative to reduce the size of the tumor and the formation of blood vessels. Moreover, several other regulatory elements were found to modulate MMP-9 levels, such as the activator protein 1 (AP-1) and p38 [24]. In addition to adenosine's stimulation on the expression of MMP-9, some other conditions - like CD73 expression or hypoxic microenvironment, for instance - also enhance the production and expression of MMP-9. Interestingly, Gessi et al. [24] also found out that there was also a modest increase of TIMP-1, a metallopeptidase inhibitor, after the addition of Ado and an A3 agonist, suggesting a compensatory regulation loop.

Secondly, MRP1 is a member of the ATP-binding cassette (ABC) transporter superfamily and is responsible for the acquisition of the MDR phenotype in GBM cells [20,27]. This phenotype was seen in both stem and differentiated GBM cells and is responsible for making them less responsive to pharmacological treatments, like chemotherapy. Due to this effect, MRP1 expression is directly correlated with a poor prognosis for patients [27]. A3AR is mainly responsible for this effect, through the pathways previously described. Curiously, according to Torres et al. [27], the researchers observed that Multiple Drug Resistance Protein-1 is more present in Glioblastoma Stem Cells (GSCs) than in adherent cells. In addition, they found that GSCs have an intrinsic ability to produce extracellular adenosine and increase expression of ARs, specially A3AR. Inhibition of MRP1 activity may be a therapeutic target to increase cell sensitivity to antineoplastic drugs.

Hypoxia, as said, is one of the key factors for the development of tumors. While in healthy brain tissue O2 levels range from 2,5 to 12,5%, in tumor they decrease to 0,1-2,5% [25,35]. Hypoxia is associated with invasiveness and angiogenesis, but even though there is an extensive blood vessels network in tumor mass, allowing its growth and resistance to treatment, the formed blood vessels are often disorganized and tortuous, making oxygen distribution deficient and favoring the hypoxic microenvironment to persist [26,36]. In a study conducted by Rocha et al. [26], the effect of hypoxia on the generation of extracellular adenosine and on the expression of A3AR was evaluated, for this purpose U87MG Glioblastoma stem cells (GSCs) were cultured in 0.5% O2. The results of this study suggest that, in hypoxia, A3AR can be activated by high levels of extracellular adenosine in U87MG GSCs.

In early hypoxia, Ado up-regulates the hypoxia-inducible factor 1a (HIF-1a), which induces the expression of ectonucleotidases - mainly ecto-5'-nucleotidase- and vascular

endothelial growth factor (VEGF), responsible for pro-angiogenic effects, proliferation and migration of endothelial cells (ECs) [24–26]. Once hypoxia becomes a chronic condition for GSCs, there is an increase in the expression of HIF-2a, which appears to strongly regulates the levels of prostatic acid phosphatase (PAP), important in the production of extracellular adenosine, migration and invasion of GSCs [25]. In addition, protein levels of vimentin, FAK and N-cadherin (proteins related migration and invasion), have been observed to increase in hypoxia and decrease when A3AR blockade[25]. The same was seen with the transcription factors TWIST and SNAIL, responsible for invasiveness and the Epithelial Mesenchymal Transition (EMT) activation [25]. Furthermore, when blocking A3AR with a selective A3AR antagonist, a reduction in the differentiation of GSCs to endothelial cells in hypoxia situations was noted [25]. This suggests that activation of A3AR in hypoxia may regulate the differentiation of GSCs in endothelial cells.

In contrast with the majority of the researches, a study by Vincenzi et al. [28] points out that the activated A3ARs may have an anti-tumor action. One of the objectives of this study was to verify whether the use of pulsed electromagnetic fields would affect the density and affinity of A3ARs in rat cortical neurons, concluding that the density of A3ARs increases considerably. It was shown that, when A3ARs were activated by the agonist CI-IB-MECA in the presence of a pulsed electromagnetic field, there was a significant augmentation in p53 expression, indicating a cytotoxic effect on tumor cells. Other results found on the study include the inhibition of NF-kB and Wnt pathways, which play a critical role in carcinogenesis, decreased [3H]-Thymidine incorporation and increased lactate dehydrogenase and caspase-3 levels, but these findings still need further investigation.

CONCLUSION

This literature review concludes that:

- GBM cells have higher levels of cellular adenosine and A3AR expression when compared to non-tumor cells;
- There is positive regulation of MMP-9 through the beta-gamma subunits of the Gi protein coupled to the A3AR receptor that stimulate signaling-related pathways by the tyrosine-kinase receptor signaling by the tyrosine-kinase receiver. In this way, the use of an A3AR antagonist appears to be able to decrease tumor invasion and angiogenesis processes to which

MMP-9 is involved, leading to a reduction in tumor size and also the formation of blood vessels. However, further studies are needed to confirm this new possibility of treatment

- There is also stimulation by the beta-gamma subunits of Gi protein coupled to A3AR of tyrosine-kinase receptor-related pathways that positively modulate MRP1 receptor expression. Thus, inhibition of the MRP1 receptor that can possibly also be done through the antagonization of A3AR may be an alternative to increase the sensitivity of these tumor cells to antineoplastic drugs. However, further studies are needed for this to be truly proven and its applicability verified.
- We believe that all the findings gathered in the last few years through studies such as the ones presented in this review, yet still restricted, bring hope to a promising target for the treatment of patients with glioblastoma multiforme. There is, therefore, the possibility that a new therapeutic approach, originated from these initial information and ideas, will bring, in a near future, a decrease in the mortality rate from the disease or at least an increase in the patients' survival and quality of life.

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