Divide et Impera: Drp1-mediated Mitochondrial Fission in Glioma Malignancy

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Mitochondria are pivotal organelles involved in vital cellular functions, including energy generation, reactive oxygen species and calcium signaling, as well as intermediate biosynthesis. They are dynamic organelles that adapt their shape, size, and distribution to changes in intracellular conditions, being able to divide, fuse, or move along the cell, processes known as mitochondrial dynamics. Mitochondrial dynamics are involved in cell division and migration, as well as maintenance of pluripotency in stem (non-differentiated) cells. Thus, its central role in carcinogenesis is not surprising. Particularly, mitochondrial dynamics have been found to be pivotal to the development of gliomas, a lethal group of tumors developed from glial cells, which are nervous system cells that provide support to neurons. Unfortunately, prognosis of glioma patients is poor, most of them do not survive more than five years after diagnosis. In this context, it is fundamental to understand the cellular mechanisms involved in this pathology, in order to develop an appropriate clinical approach. As previously mentioned, mitochondrial dynamics is central to glioma development, particularly, mitochondrial division (fission) and one of its central effectors, dynamin-related protein 1 (Drp1†), have been observed to be enhanced in gliomas and involved in the maintenance of stem cells (which initiate and maintain the tumor), as well as in migration and invasiveness, being central to gliomagenesis. In this review, we discuss the findings on mitochondrial fission role in these processes, further, we analyze the potential use of Drp1 as a novel prognostic biomarker in glioma patients.

INTRODUCTION

Mitochondria are central cellular organelles that accomplish many of the essential cellular functions, including oxidative phosphorylation (OXPHOS), reactive oxygen species (ROS), and calcium (Ca²⁺) signaling, as well as intermediate metabolite synthesis required for cell growth and motility [1]. These organelles can be found as small units or as a complex network and it is not surprising that mitochondrial shape is tightly related to its function [2]. Consequently, it has been established that shape, size, and location of mitochondria are outputs of the cellular ability to adapt and supply the energy required for survival, proliferation, and migration [3].

The mechanisms by which mitochondria can divide, fuse, or move along the cells are known as mitochondrial dynamics. Notably, these processes are needed to

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†Abbreviations: Drp1, dynamin-related protein 1; OXPHOS, oxidative phosphorylation; OPA1, optic atrophy protein 1; IMM, inner mitochondrial membrane.

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rearrange or exchange deoxyribonucleic acid (DNA) and proteins between mitochondria, redistribute mitochondrial content within the cell, and also isolate dysfunctional parts, leading to their recycling [2,4,5].

Particularly, the merging of mitochondria is an essential strategy to enhance the membrane potential and increase OXPHOS under stress circumstances, such as nutrient deprivation, moreover, generating a complex network helps to avoid mitochondrial degradation by mitophagy [1]. Tethering of outer mitochondrial membrane is carried out by mitofusins (Mfn) 1 and 2, which mix the lipid bilayers when they are close enough. On the other hand, the optic atrophy protein 1 (OPA1), which is a dynamin-like GTPase, binds the inner mitochondrial membrane (IMM) and regulates the cristae remodeling after being activated by some metalloproteinases, such as the ATP-dependent AAA+ protease (YME1L) or the ATP-independent protease (OMA1) (Figure 1a) [1,6].

Simultaneously, fragmented mitochondria are necessary to distribute these organelles within the cell to regions of higher energy demand or for cell division [3,7]. Fragmentation is mainly performed by the dynamin 1-like protein (Drp1) [8]. This protein is as a GTPase, conserved in metazoan, which forms helices around some mitochondrial regions and then couples GTP hydrolysis with mitochondrial membrane constriction. Drp1 is mainly found in the cytosol and recruited to mitochondria by outer mitochondrial membrane receptors. In metazoan, these receptors include the mitochondrial fission protein 1 (Fis1), the mitochondrial fission factor (Mff), and the ganglioside-induced differentiation associated protein 1 (GDAP). Furthermore, in chordate, two other receptors bind Drp1, namely, mitochondrial division proteins (MiD) 49 and 51 [8].

Notably, Drp1 activity is regulated by post-translational modifications, mainly by phosphorylation: while serine (Ser) 616 residue is an activation site, Ser637 residue is an inhibition site [9,10]. Further, Drp1 is regulated by ubiquitination and SUMOylation [11]. About the former, ubiquitin is a 76-aminoacid polypeptide, which is bound to lysine residues on target proteins [11]. Ubiquitination may lead to proteosomal degradation of target proteins or may also mediate interactions with other proteins [11]. Drp1 has been reported to be ubiquitylated by the E3 ligase Parkin, process that leads to Drp1 degradation and mitochondrial fission blockage [12]. Further, Drp1 is also ubiquitylated by the ligase MARCH5, which leads to Drp1 degradation [13,14]. However, MARCH5-mediated Drp1 ubiquitination was observed to be necessary for mitochondrial fission [15]. Accordingly, MARCH5-mediated ubiquitination was proposed to participate in the correct assembly of Drp1 helices or in the disassembly of fission complexes [15]. Evidently, more studies on this regard are needed.

Regarding SUMOylation, this post-translational modification consists in the addition of small ubiquitin-like modifier (SUMO) proteins and regulates conformation and function, as well as interactions and localization of target proteins [11]. In Drp1 SUMOylation, the enzymes ubiquitin-like protein SUMO-conjugating enzyme 9 (Ubc 9) and mitochondrial-anchored protein ligase (MAPL) have been described to participate as E2 and E3 ligases, respectively [16,17].

Drp1 has been observed to be bound to SUMO-1, -2 and -3 proteins [17]. Notably, binding to each one has different effects on fission. SUMO-1 binding favors fission, by enhancing Drp1 recruitment to mitochondria [18]. Importantly, the Sentrin specific protease (SENP) 5, which removes SUMO-1, also favors fission [19]. As a matter of fact, this protease resides in nucleoli during interphase, but is released and recruited to mitochondria in mitosis, promoting mitochondrial fragmentation in this step of the cell cycle, thus allowing segregation of these organelles [19]. SENP5 effect was proposed to be mediated by destabilization of Drp1 binding to mitochondrial membrane, which may favor oligomerization and subsequent fission. SENP5 is thought to create a Drp1 labile pool able to oligomerize around fission sites [19].

Concerning SUMO-2 and -3, binding of these proteins hamper mitochondrial fission [20], at least, by blocking Drp1 interaction with Mff and recruitment to mitochondria [21]. In line with this, the protease SENP3, known to remove these modifications, promotes mitochondrial fission, by enhancing Drp1 binding to mitochondria [21]. Moreover, SENP5 removes SUMO-2 and -3 as well [22], which may also account for its fission-promoting effect. In summary, phosphorylation, ubiquitination, and SUMOylation are important Drp1 modifications that finely regulate its activity and mitochondrial fission.

Notably, Drp1 helices are smaller than mitochondria, suggesting that a previous morphological event that constricts mitochondria occurs. Noteworthy, this event is suggested to be carried out by the endoplasmic reticulum (ER) [8], which promotes actin polymerization towards mitochondria, at ER-mitochondria contact sites [23,24]. Notably, actin filaments were observed to bind myosin II [25], which was recently proposed to pull actin filaments and subsequently constrict mitochondria. Drp1 would then polymerize at these constriction sites and, by its GTPase activity, further constrict mitochondria and mediate fission.

It is important to mention that, recently, a central role for the dynamin protein 2 (Dyn2) in mitochondrial fission was proposed. This protein is also a GTPase which was observed to transiently bind at mitochondrial Drp1-bound sites, in different mammalian cells, including human cells [26]. Noteworthy, Dyn2 deletion was observed to block the final scission in mitochondrial fission. Following de-
letion, constrictions between assembled Drp1 populations were found, but mitochondria were not divided [26]. Remarkably, after mitochondrial fission, the Drp1 helix separates into the two daughter mitochondria and changes on actin dynamics have been proposed to mediate this final segregation [27]. Further, actin is the only known binding partner of Dyn2 that is present in mitochondria [28]. Hence, Dyn2 may regulate actin-mediated Drp1 helix splitting and, thus, be necessary for final mitochondrial membrane scission. Nevertheless, further investigation in this regard is needed.

MITOCHONDRIAL DYNAMICS IN GLIOMA DEVELOPMENT

As mitochondrial dynamics are involved in cell proliferation and are also relevant in maintenance of pluripotency in stem cells and cell movement [29,30], its important role in cancer development is not surprising. Concerning this review, these processes are relevant to the development and aggressiveness of gliomas, a group of tumors with elevated lethality [31]. Gliomas are tumors developed from glial cells, which are nervous system cells that provide support to neurons [32]. They account for the 81 percent of malignant brain tumors [31] and, unfortunately, have a poor prognosis (Table 1), with a high 5-year mortality after diagnosis. For instance, the survival rate for glioblastoma, the most common type of glioma, is of 5 to 9 percent at five years after diagnosis [33]. In this context, it is central to understand the cellular mechanisms involved in the development of these pathologies in order to develop appropriate therapeutic approaches.

As mentioned above, mitochondrial dynamics are involved in glioma development. Particularly, fission has been reported to be enhanced in this process [34] and participate in the maintenance of stem cells (involved in tumor formation and growth, as well as relapse), invasion and migration. The following sections in this review discuss the role of mitochondrial fission in these phenomena. Additionally, we discuss whether Drp1 (expression, levels or activating phosphorylation) could be used as prognostic biomarkers in glioma patients.

MITOCHONDRIAL FISSION AND STEMNESS

Cancer stem cells are an important cancer cell sub-
population, which are known to maintain the tumor and have been proposed to begin its formation, although, this last issue remains controversial [35]. These properties are given by cancer stem cells capacity to self-renew and also to differentiate into different cancer clones. Moreover, these cells are immortal and able to evade anticancer immune response [36]. Importantly, cancer stem cells also mediate recurrence after therapy, since they are chemo and radioresistant [37,38].

Mitochondrial morphology of glioma stem cells was found to be more fragmented than morphology of non-stem cells [36], a phenomenon that was found to be mediated by enhanced Drp1 activation [36], suggesting that mitochondrial fission is involved in glioma cell stemness (Figure 2). Additionally, in glioma cell culture, inhibition of Drp1 resulted loss of stem cell proliferation, self-renewal, and tumor formation capacity, evidencing the central role of this protein in stemness [36]. In this regard, data on both mitochondrial fission-dependent and independent maintenance of stemness by Drp1 exists. Concerning the former, Drp1 has been observed to participate in mitochondrial fission and subsequent symmetrical distribution upon cytokinesis of several cell types [39]. Therefore, Drp1 may maintain stemness by supporting cell division. Moreover, an interesting study on mammary stem cells reported that mitochondrial fission is necessary for an asymmetrical mitochondrial distribution to daughter cells, where aged or deficient mitochondria are segregated to the more differentiated cells, whereas healthy mitochondria remain in the stem daughter cells [40]. This mechanism contributes to maintain a healthy stem cell population and Drp1 effect on stemness may also be mediated by this process.

About the mitochondrial fission-independent role of Drp1 in stemness, Drp1 was found to block adenosine monophosphate activated protein kinase (AMPK), a protein involved in a complex system that is in charge of monitoring the ATP levels and regulating the processes involved on ATP-utilizing pathways and energy homeostasis [41]. Drp1 effect on AMPK was observed to be necessary for the maintenance of stem cell characteristics [42]. Moreover, AMPK is known to induce glioma cells differentiation by activating the transcription factor forkhead box protein O3 (FOXO3) [43]. As a matter of fact, AMPK is also known to induce other stem cells differentiation under stress circumstances [44]. Notably, stemness is energetically expensive [44], hence, inducing differentiation may be a response under energetic stress. In gliomas, as the tumor grows, some cells become far from the vasculature and thus depleted of nutrients, which results in energetic stress [45]. Therefore, under these circumstances, Drp1 upregulation (which activity is further increased in glioma stem cells as compared to non-stem ones) must have resulted beneficial (or advantageous) to maintain stem cells population.

Generally, in glioma cells, Drp1 has been reported to be upregulated [42,46]. However, its activating phosphorylation, as well as mitochondrial fission, were found to be higher in glioma stem cells, compared to non-stem cells. Regarding the mechanisms mediating this difference, two upstream regulators have been described:

Cyclin dependent kinase 5 (CDK5), which is part of a family of proteins that regulates the cell cycle and gene transcription. In particular, this kinase is usually involved in neural development and migration [47]. CDK5 phosphorylates Drp1 in its serine 616 residue, resulting in its activation. Notably, this kinase was observed to be upregulated in glioma stem cells, as compared to non-stem cells [36].

Calcium calmodulin kinase 2 (CAMK2), is an effector of the Ca \(^{2+}\) signaling mostly expressed in neurons [48], it phosphorylates Drp1 in its serine 637 residue, resulting in its inactivation. Notably, this kinase was observed to be downregulated in stem cells, as compared with non-stem cells [42]. Clearly, these differences may mediate dissimilarities in Drp1 activity found in glioma stem and non-stem cells.

Evidently, more studies are needed to determine Drp1 and mitochondrial fission role in stemness, as well as the pathways involved in their regulation. Especially, it would be interesting to determine whether an asymmetrical mitochondrial distribution occurs when a glioma stem cell gives rise to a differentiated cell and a stem cell.

### MITOCHONDRIAL FISSION IN INVASION AND MIGRATION

| Type of glioma                        | 1-year Relative Survival (%) | 5-year Relative Survival (%) |
|--------------------------------------|------------------------------|------------------------------|
| Glioblastoma                         | 41-50                        | 5-9                          |
| Non-glioblastoma astrocytomas        | 71-78                        | 44-51                        |
| Oligodendrogial tumors               | 90-92                        | 64-74                        |
| Ependymoma                           | 93-95                        | 84-89                        |
| Other gliomas                        | 65-70                        | 36-45                        |
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Invasion represents an advanced glioma stage. It is important to mention that this aspect is slow in low grade glioma, but fast and an important hallmark in glioblastoma (high grade glioma). Notably, this phenomenon is related to poor prognosis, since a tumor can be removed by surgery but cells that have migrated and invaded adjacent tissues persist, proliferate, and constitute a new tumor [49].

Cell migration and subsequent invasion are believed to result from low oxygen and nutrient availability [50]. In glioblastoma, it has been described that, as a tumor progresses, a central anoxic zone develops, inducing necrosis in cells on this area [45]. On the other hand, in the perinecrotic zones hypoxia is set and promotes cell migration and invasion of adjacent tissue [45,50]. Importantly, hypoxia has been observed to induce migration by modulating mitochondrial dynamics (Figure 3). Hypoxia was reported to increase Drp1 mRNA and protein levels, thus promoting fission, which was found to be necessary for migration [51]. Mitochondrial fission has been found to be central for this process, since it participates in the formation of lamellipodia, which are cytoplasm protrusions that allow cell movement and are formed by actin polymerization [52]. For lamellipodia formation to occur, mitochondria need to be fragmented and redistributed towards the cell periphery, in order to provide the high-energy demands of cytoskeleton remodeling [53]. Therefore, mitochondrial fission is pivotal to this process.

Concerning the mechanisms involved in Drp1 modulation in gliomas, regulation of expression and activity levels has been described (Figure 3). About the former, Drp1 expression was observed to be enhanced by the transcription factor hypoxia inducible factor 1 (HIF1), that is central in the hypoxic response [54]. Hypoxia induces HIF1 stabilization and activation, thus promoting the transcription of its target genes, which are involved in hypoxic response processes, such as glucose uptake enhancement and angiogenesis [55]. Notably, in glioma cells, the HIF1 transcription factor was found to mediate Drp1 upregulation, process that would be part of the hypoxic response, since it mediates cell migration to more oxygenated areas [56].

Importantly, Drp1 expression was also observed to be augmented by the protein disrupted-in-schizophrenia 1 (DISC1) [57]. DISC1 is a multi-compartmentalized protein, upregulated and mainly found in mitochondria in glioma cells [58]. This protein is highly relevant to mitochondrial function, being central in adenosine triphosphate (ATP) production and calcium buffering [58]. Furthermore, DISC1 is pivotal to mitochondrial trafficking through the cytoskeleton, since it allows the interaction between the motor and adaptor proteins [58]. In glioma
cells, DISC1 was observed to increase Drp1 expression and protein levels, as well as to participate in cell migration [59]. Perhaps, this protein may direct a program that involves mitochondrial fission and subsequent trafficking to the cell periphery, which allows lamellipodia formation and glioma cell migration (Figure 3). This regulatory mechanism evidences that not only do enhanced mitochondrial fission, but also enhanced mitochondrial interaction with cytoskeleton and subsequent transport, may be involved in glioma malignancy.

Importantly, the mechanisms involved in DISC1 upregulation in gliomas, as well as in DISC1-enhanced Drp1 expression and levels remain unknown and, thus, studies on this regard are needed. It would be also interesting to establish whether there are DISC1 changes, under hypoxic conditions, in glioma cells.

Regarding regulation of Drp1 activity, the nuclear factor-κB (NF-κB) inducing kinase (NIK), a non-canonic pathway activator of the inflammatory response through NF-κB [60], was found to interact with Drp1, promoting its mitochondrial localization, thus enhancing its activity in glioma cells. Furthermore, this kinase was observed to enhance Drp1 activating phosphorylation (in S616 residue). Notably, NIK also mediated mitochondrial trafficking to glioma cell periphery [53]. Therefore, its mechanism of action in gliomas may be similar to that of DISC1, promoting mitochondrial fission and its subsequent distribution to the cell periphery. Concerning the mechanisms by which NIK promote Drp1 phosphorylation, this kinase is known to activate the extracellular signal-regulated kinase 2 (ERK2) [61], a known Drp1 inductor, in cancer cells. Interestingly, NIK has been reported to be positively regulated by ROS [62], which production is known to be increased under hypoxia [63]. Therefore, NIK activation may occur under hypoxic conditions and also contribute to migration and evasion of hypoxia by glioma cells.

Perhaps, Drp1-mediated fission is also regulated by the tumor necrosis factor receptor-associated protein 1 (TRAP1; Figure 3), a chaperone known to be involved in gliomagenesis [64]. Importantly, TRAP1 has been previously reported to maintain glioma cells glycolysis [64]. Furthermore, this protein was observed to augment Mff mitochondrial levels and fission in glioma cells. This effect on fission may have resulted from Mff-enhanced Drp1 mitochondrial localization [65]. Noteworthy, the expression of TRAP1 has been reported to be enhanced by hypoxia [66]. Consequently, hypoxia may augment TRAP1 expression, promoting its activity, which in turn
would direct a response to hypoxia in glioma cells, which may involve promotion of anaerobic metabolism and Drp1-mediated migration.

Finally, Drp1 not only participates in mitochondrial redistribution in glioma cell migration, but also has another functional role in this process. Drp1 was found to augment levels of the GTPase Ras homolog gene family, member A (RhoA; Figure 3), which is central to cell movement. This effect was observed to be mediated by interaction with this protein, [46] hence, Drp1 may stabilize RhoA. The latter is known to be central in cell body retraction, under cell migration [67]. Furthermore, RhoA was found to be needed for lamellipodia formation in glioblastoma cells [68]. RhoA, by activating its downstream effector, the Rho-associated protein kinase (ROCK), regulates contractile actomyosin filaments assembly, and then allows cell body retraction, thus being central to migration. Therefore, Drp1 not only mediates glioma cell migration by enhancing mitochondrial fission, but also by upregulating RhoA [46].

**DRP1 AS A PROGNOSTIC BIOMARKER**

As previously mentioned, in this final section, we discuss the potential use of Drp1 as a prognostic marker in glioma patients. Determining prognosis is relevant in cancer patients, since it indicates if anticancer therapy is appropriate. Further, it relieves anxiety of patients caused by uncertainty and can be useful in end-of-life care planning.

Several molecules have been evaluated for prognostic value in gliomas. Currently, the most used biomarker is isocitrate dehydrogenase (IDH) status [69]. Some gliomas have been observed to present an IDH mutation that modifies the activity of this enzyme, blocking its forward reaction (isocitrate conversion to alpha-ketoglutarate) and modifying the reverse one, leading to the production of the oncometabolite 2-hydroxyglutarate (2-HG) instead of isocitrate. IDH status has been reported to have an important prognostic value, because the mutation negatively associates with glioma aggressiveness and grade. This prognostic value has been attributed to the mutation effect on redox state, since the production of 2-HG consumes nicotinamide adenine dinucleotide phosphate (NADPH), a relevant compound for the antioxidant system [70]. A glioma malignant phenotype is able to evolve when an efficient antioxidant system could counteract ROS produced by clones with an elevated proliferative capacity [71]. Since IDH mutation affects the antioxidant system, it compromises malignant evolution and, thus, confers a better outcome. Further, 2-HG promotes HIF1 degradation, which, as previously mentioned, is central to glioma cells migration and invasion [72]. Therefore, IDH mutation-enhanced 2-HG production reduces glioma aggressiveness. Hence, these effects make IDH status efficient at informing prognosis, however, more useful biomarkers could be developed. Biomarkers that also provide other relevant information may be found. For instance, we can search for a continuous (instead of discrete, as the IDH mutation) biomarker that provides more accurate information and, besides informing on prognosis in each grade of glioma, supports grading. Notably, Drp1 expression or protein levels, as well as phosphorylation status, are continuous parameters that, as previously described, are related to glioma aggressiveness. Therefore, these parameters could work as novel prognostic markers, in glioma patients.

In fact, an association between Drp1 activating phosphorylation and glioblastoma (grade IV glioma) patients prognosis has been previously reported [36]. However, it remains to be determined whether a correlation between this parameter and prognosis thorough all glioma grades exists. Further, in order to determine whether this biomarker could inform on both prognosis and malignancy grade, it is necessary to establish if there exists a correlation between the continuum of Drp1 phosphorylation levels and grade. Importantly these correlations are plausible to exist since, as previously mentioned, Drp1 is related to stemness and invasiveness, characteristics that increase with glioma grade and decrease prognosis [73-76].

Notably, besides glioma grade, Drp1 biomarkers may also give precise information on invasiveness and indicate whether surgical resection may be appropriate. Surgery is included in the standard glioma clinical approach; however, several complications may occur, namely, vascular or health brain tissue damage, hematomas, seizures, hydrocephalus, cerebrospinal fluid leakage, infections, deep vascular thrombosis, among others [77]. In this context, if glioma is highly invasive, as indicated by elevated Drp1 biomarkers, surgery may result in more disadvantages than benefits, thus other alternatives may be looked for.

Additionally, Drp1 biomarkers would possess another advantage over IDH status. Importantly, IDH screening presents the problem that not all tumors have the mutation in the same amino acid. Commonly, the IDH mutation occurs in the amino acid 132, consequently, in clinics, only IDH mutations on this residue are looked for, therefore, false negative results may be obtained [78]. Noteworthy, this problem would not be found by determining Drp1 expression, levels or activating S616-phosphorylation. Consequently, using Drp1 biomarkers should be considered, since it would provide accurate prognosis information, as well as additional data.

Finally, it is important to mention that Drp1 expression and protein levels could also be employed as prognostic biomarkers. However, it would be more accurate to use activating phosphorylation levels, because the former could be augmented without an increase in Drp1 activity.
and a fragmented mitochondrial morphology.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Mitochondrial fission is enhanced in gliomas and, as evidenced, it is central to their development, since fission participates in migration and invasion, as well as in stem cell maintenance. Therefore, fission should be considered as a malignancy advantage in glioma cells. Importantly, this information ought to be employed in clinics, for instance, to develop accurate and novel Drp1-based prognostic biomarkers. Since Drp1 is involved in notable processes of gliomagenesis and, is also a continuous parameter, it may be useful not only in prognosis, but also in grading. Therefore, investigation in this regard may be carried out in order to establish the correlation between glioma grade and the continuum of Drp1 expression, levels, or phosphorylation. Further, information on mitochondrial dynamics dysregulation may also be used in antineoplastic drugs development, since blocking fission in glioma cells may be useful. Importantly, this inhibition may be selective since hampering fission in neurons would have fatal effects on synapses.

Interestingly, Drp1 also participates in peroxisome fission [79] and these organelles have been reported to have a tumorigenic role [80]. For instance, they are known to participate in the synthesis and secretion of pro-invasive mediators [81,82]. In this regard, Drp1-mediated peroxisomal fission and redistribution to the cell periphery may also provide an advantage for cancer cells. However, information on peroxisomal dynamics in cancer is scarce and, in gliomas, unavailable. Therefore, its role in carcinogenesis and, particularly, in gliomagenesis must be investigated.

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