YALE JOURNAL OF BIOLOGY AND MEDICINE 92 (2019), pp.423-433.

REVIEW

YALE JOURNAL OF BIOLOGY AND MEDICINE
YJBM
CELEBRATING 90 YEARS 1928–2018

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

Dianelena Eugenio-Pérez, Alfredo Briones-Herrera, Elena Martínez-Klimova, and José Pedraza-Chaverri*

Departamento de Biología, Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Mexico City, Mexico

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 (Ca^{2+}) 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

*To whom all correspondence should be addressed: José Pedraza-Chaverri, Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Mexico City, 04510 Mexico; Email: pedraza@unam.mx.

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

Keywords: organelles, mitochondria, glioma, cancer, stem cells, Drp1

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 mitochondrion, 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-

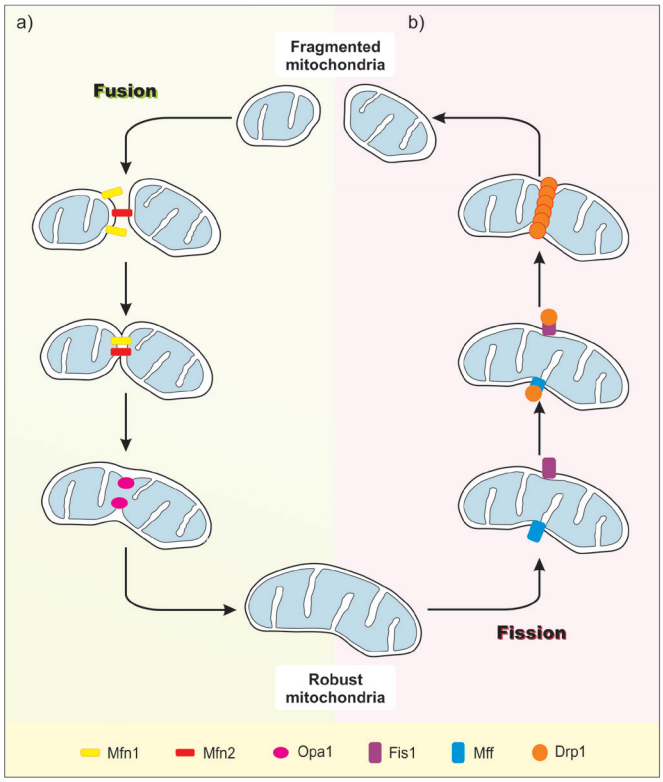

Figure 1. Mitochondrial dynamics as opposite processes. (**a**) Fusion originates robust mitochondrial leading to mitochondrial networks, it is carried out by Mitofusins 1 and 2 (Mfn1, Mfn2) and the optic atrophy 1 protein (OPA1). (**b**) Fission results in fragmented mitochondria, process that is performed by the dynamin 1-like protein (Drp1) through its canonic receptors: the mitochondrial fission protein 1 (Fis1) and the mitochondrial fission factor (Mff).

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-

Table 1. Relative survival rates of different types of glioma (years 2000-2014 in the United States). Data was obtained from Ostrom *et al.* 2018 [31].

Type of glioma	1-year Relative Survival (%)	5-year Relative Survival (%)
Glioblastoma	41-50	5-9
Non-glioblastoma astrocytomas	71-78	44-51
Oligodendroglial tumors	90-92	64-74
Ependymoma	93-95	84-89
Other gliomas	65-70	36-45

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. 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

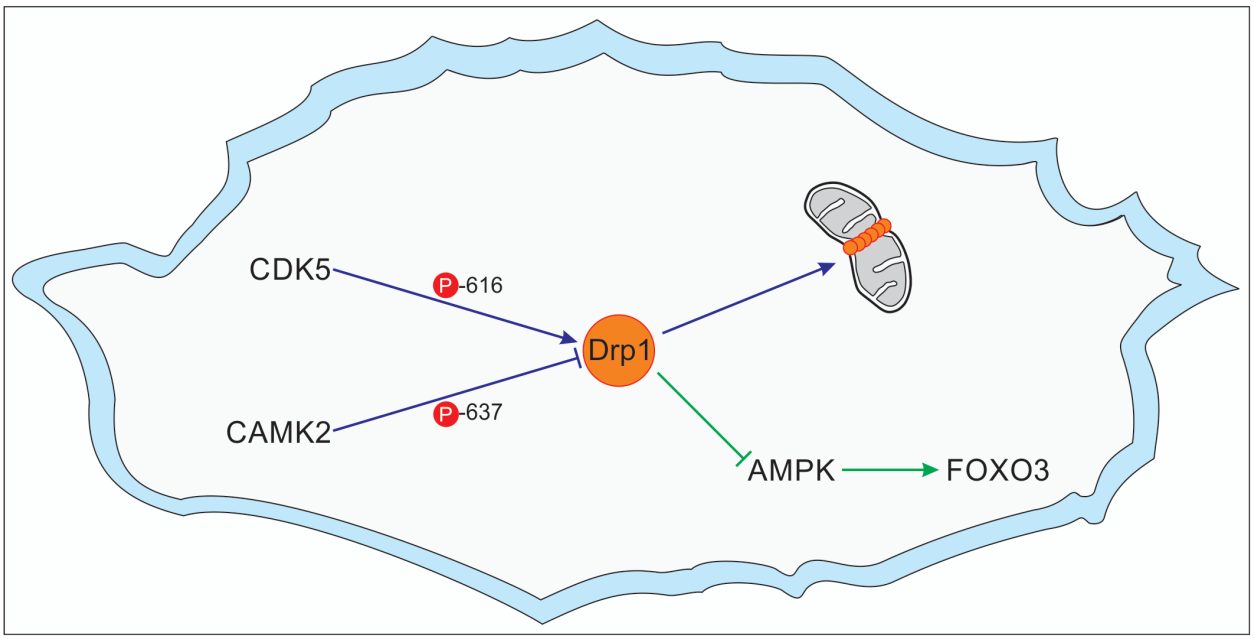

Figure 2. Role of the dynamin 1-like protein (Drp1) on glioma stemness. Blue connectors indicate phenomena involved in mitochondrial fission-dependent Drp1 effects on stemness; while the cyclin dependent kinase 5 (CDK5) mediates the activating S616 phosphorylation, the calcium calmodulin kinase 2 (CAMK2) phosphorylates Drp1 on S637 hampering its activity. Green connectors show the inhibition of adenosine monophosphate-activated protein kinase (AMPK) and subsequent blockage of forkhead box protein O3 (FOXO3), as the known mitochondrial fission-independent effects.

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

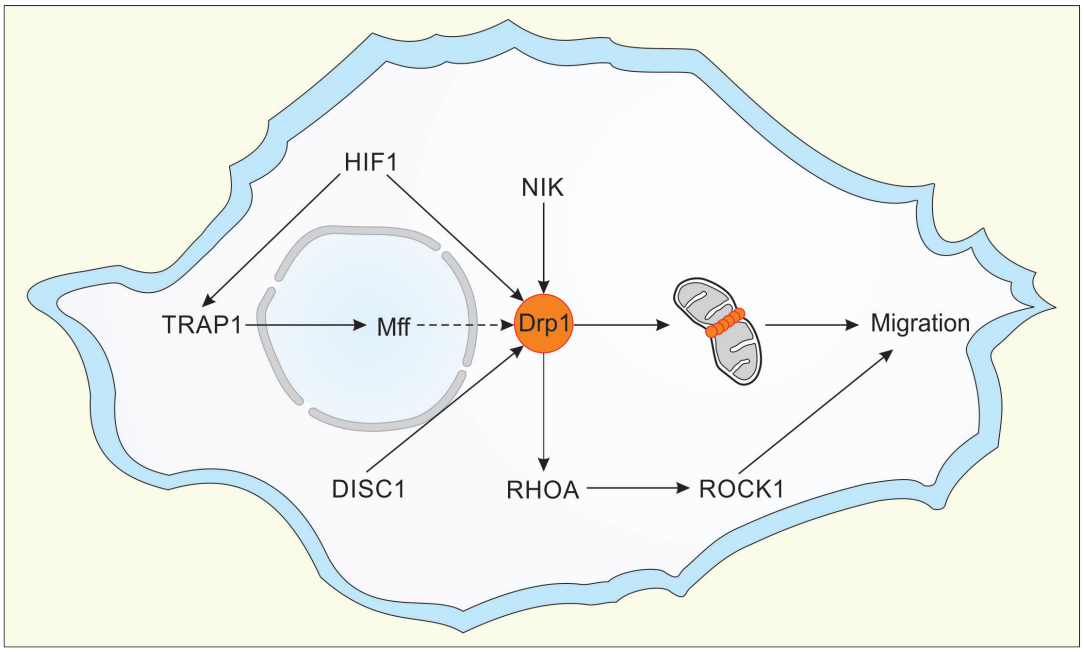

Figure 3. Role of mitochondrial fission in glioma invasiveness. Several factors can activate the activity of the dynamin 1-like protein (Drp1) and consequently the cell migration on glioma cells. First, the hypoxia inducible factor 1 (HIF1) can augment Drp1 transcription, further, it can also induce the tumor necrosis factor receptor-associated protein 1 (TRAP1) that was observed to augment the levels of the mitochondrial fission factor (Mff) resulting in higher recruitment of Drp1 to mitochondria, a similar effect was related to the protein disrupted-in-schizophrenia 1 (DISC1). The nuclear factor-κB inducing kinase (NIK) has also been proven to enhance the mitochondrial fission activity of Drp1. Once activated Drp1 it can interact with the GTPase Ras homolog gene family, member A (RHOA) and then induce migration through the Rho-associated protein kinase (ROCK).

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 location, 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 synapsis.

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.

REFERENCES

1. Bhargava P, Schnellmann RG. Mitochondrial energetics in the kidney. Nat Rev Nephrol. 2017 Oct;13(10):629–46.
2. Serasinghe MN, Chipuk JE. Mitochondrial Fission in Human Diseases [Internet]. Handb Exp Pharmacol. 2017;240:159–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28040850
3. Trotta AP, Chipuk JE. Mitochondrial dynamics as regulators of cancer biology [Internet]. Cell Mol Life Sci. 2017 Jun;74(11):1999–2017. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28083595
4. Bhargava P, Schnellmann RG. Mitochondrial energetics in the kidney [Internet]. Nat Rev Nephrol. 2017 Oct;13(10):629–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28804120
5. Jackson JG, Robinson MB. Regulation of mitochondrial dynamics in astrocytes: Mechanisms, consequences, and unknowns [Internet]. Glia. 2018 Jun;66(6):1213–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29098734
6. Frezza C, Cipolat S, Martins de Brito O, Micaroni M, Beznoussenko GV, Rudka T, et al. OPA1 controls apoptotic cristae remodeling independently from mitochondrial fusion [Internet]. Cell. 2006 Jul;126(1):177–89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16839885
7. Senft D, Ronai ZA. Regulators of mitochondrial dynamics in cancer [Internet]. Curr Opin Cell Biol. 2016 Apr;39:43–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26896558
8. Kraus F, Ryan MT. The constriction and scission machineries involved in mitochondrial fission. J Cell Sci. 2017 Sep;130(18):2953–60.
9. Chang CR, Blackstone C. Cyclic AMP-dependent protein kinase phosphorylation of Drp1 regulates its GTPase activity and mitochondrial morphology [Internet]. J Biol Chem. 2007 Jul;282(30):21583–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17553808
10. Han XJ, Lu YF, Li SA, Kaitsuka T, Sato Y, Tomizawa K, et al. CaM kinase I alpha-induced phosphorylation of Drp1 regulates mitochondrial morphology [Internet]. J Cell Biol. 2008 Aug;182(3):573–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18695047
11. Pagliuso A, Cossart P, Stavru F. The ever-growing complexity of the mitochondrial fission machinery. Cell Mol Life Sci. 2018 Feb;75(3):355–74.
12. Wang H, Song P, Du L, Tian W, Yue W, Liu M, et al. Parkin ubiquitinates Drp1 for proteasome-dependent degradation: implication of dysregulated mitochondrial dynamics in Parkinson disease [Internet]. J Biol Chem. 2011 Apr;286(13):11649–58. Available from: http://www.jbc.org/lookup/doi/10.1074/jbc.M110.144238
13. Nakamura N, Kimura Y, Tokuda M, Honda S, Hirose S. MARCH-V is a novel mitofusin 2- and Drp1-binding protein able to change mitochondrial morphology. EMBO Rep. 2006 Oct;7(10):1019–22.
14. Zhang C, Shi Z, Zhang L, Zhou Z, Zheng X, Liu G, et al. Appoptosin interacts with mitochondrial outer-membrane fusion proteins and regulates mitochondrial morphology [Internet]. J Cell Sci. 2016 Mar;129(5):994–1002. Available from: http://jcs.biologists.org/lookup/doi/10.1242/jcs.176792
15. Karbowski M, Neutzner A, Youle RJ. The mitochondrial E3 ubiquitin ligase MARCH5 is required for Drp1 dependent mitochondrial division. J Cell Biol. 2007 Jul;178(1):71–84.
16. Braschi E, Zunino R, McBride HM. MAPL is a new mitochondrial SUMO E3 ligase that regulates mitochondrial fission. EMBO Rep. 2009 Jul;10(7):748–54.
17. Figueroa-Romero C, Iñiguez-Lluhí JA, Stadler J, Chang CR, Arnoult D, Keller PJ, et al. SUMOylation of the mitochondrial fission protein Drp1 occurs at multiple nonconsensus sites within the B domain and is linked to its activity cycle [Internet]. FASEB J. 2009 Nov;23(11):3917–27. Available from: http://www.fasebj.org/doi/10.1096/fj.09-136630
18. Wasiak S, Zunino R, McBride HM. Bax/Bak promote sumoylation of DRP1 and its stable association with mitochondria during apoptotic cell death. J Cell Biol. 2007 May;177(3):439–50.
19. Zunino R, Braschi E, Xu L, McBride HM. Translocation

of SenP5 from the nucleoli to the mitochondria modulates DRP1-dependent fission during mitosis. J Biol Chem. 2009 Jun;284(26):17783–95.
20. Guo C, Hildick KL, Luo J, Dearden L, Wilkinson KA, Henley JM. SENP3-mediated deSUMOylation of dynamin-related protein 1 promotes cell death following ischaemia [Internet]. EMBO J. 2013 May;32(11):1514–28. Available from: http://emboj.embopress.org/cgi/doi/10.1038/emboj.2013.65
21. Guo C, Wilkinson KA, Evans AJ, Rubin PP, Henley JM. SENP3-mediated deSUMOylation of Drp1 facilitates interaction with Mff to promote cell death [Internet]. Sci Rep. 2017 Mar;7(1):43811. Available from: http://www.nature.com/articles/srep43811
22. Békés M, Prudden J, Srikumar T, Raught B, Boddy MN, Salvesen GS. The dynamics and mechanism of SUMO chain deconjugation by SUMO-specific proteases [Internet]. J Biol Chem. 2011 Mar;286(12):10238–47. Available from: http://www.jbc.org/lookup/doi/10.1074/jbc.M110.205153
23. Manor U, Bartholomew S, Golani G, Christenson E, Kozlov M, Higgs H, et al. A mitochondria-anchored isoform of the actin-nucleating spire protein regulates mitochondrial division [Internet]. Elife. 2015 Aug;4. Available from: https://elifesciences.org/articles/08828
24. Li S, Xu S, Roelofs BA, Boyman L, Lederer WJ, Sesaki H, et al. Transient assembly of F-actin on the outer mitochondrial membrane contributes to mitochondrial fission [Internet]. J Cell Biol. 2015 Jan;208(1):109–23. Available from: http://www.jcb.org/lookup/doi/10.1083/jcb.201404050
25. Korobova F, Gauvin TJ, Higgs HN. A role for myosin II in mammalian mitochondrial fission [Internet]. Curr Biol. 2014 Feb;24(4):409–14. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0960982213015911
26. Lee JE, Westrate LM, Wu H, Page C, Voeltz GK. Multiple dynamin family members collaborate to drive mitochondrial division [Internet]. Nature. 2016 Dec;540(7631):139–43.
27. Ramachandran R. Mitochondrial dynamics: the dynamin superfamily and execution by collusion [Internet]. Semin Cell Dev Biol. 2017. https://doi.org/10.1016/j.semcdb.2017.07.039.
28. Gu C, Yaddanapudi S, Weins A, Osborn T, Reiser J, Pollak M, et al. Direct dynamin-actin interactions regulate the actin cytoskeleton [Internet]. EMBO J. 2010 Nov;29(21):3593–606.
29. Chen H, Chan DC. Mitochondrial Dynamics in Regulating the Unique Phenotypes of Cancer and Stem Cells [Internet]. Cell Metab. 2017 Jul;26(1):39–48. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1550413117303406
30. Campello S, Lacalle RA, Bettella M, Mañes S, Scorrano L, Viola A. Orchestration of lymphocyte chemotaxis by mitochondrial dynamics [Internet]. J Exp Med. 2006 Dec;203(13):2879–86. Available from: http://www.jem.org/lookup/doi/10.1084/jem.20061877
31. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, et al. The epidemiology of glioma in adults: a "state of the science" review [Internet]. Neuro Oncol. 2014 Jul;16(7):896–913. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24842956
32. Weller M, Wick W, Aldape K, Brada M, Berger M, Pfister SM, et al. Glioma. Nat Rev Dis Primers [Internet]. 2015;1:15017. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27188790
33. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, et al. The epidemiology of glioma in adults: a "state of the science" review. Neuro Oncol. 2014 Jul;16(7):896–913.
34. Yin M, Lu Q, Liu X, Wang T, Liu Y, Chen L. Silencing Drp1 inhibits glioma cells proliferation and invasion by RHOA/ ROCK1 pathway [Internet]. Biochem Biophys Res Commun. 2016 Sep;478(2):663–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27495873
35. Chen K, Huang YH, Chen JL. Understanding and targeting cancer stem cells: therapeutic implications and challenges [Internet]. Acta Pharmacol Sin. 2013 Jun;34(6):732–40. Available from: http://www.nature.com/doifinder/10.1038/aps.2013.27
36. Xie Q, Wu Q, Horbinski CM, Flavahan WA, Yang K, Zhou W, et al. Mitochondrial control by DRP1 in brain tumor initiating cells [Internet]. Nat Neurosci. 2015 Apr;18(4):501–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25730670
37. Chen J, Li Y, Yu TS, McKay RM, Burns DK, Kernie SG, et al. A restricted cell population propagates glioblastoma growth after chemotherapy [Internet]. Nature. 2012 Aug;488(7412):522–6. Available from: http://www.nature.com/articles/nature11287
38. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response [Internet]. Nature. 2006 Dec;444(7120):756–60. Available from: http://www.nature.com/articles/nature05236
39. Chen H, Chan DC. Emerging functions of mammalian mitochondrial fusion and fission [Internet]. Hum Mol Genet. 2005 Oct;14 Spec No. 2(Spec No):R283–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16244327
40. Katajisto P, Döhla J, Chaffer CL, Pentinmikko N, Marjanovic N, Iqbal S, et al. Stem cells. Asymmetric apportioning of aged mitochondria between daughter cells is required for stemness [Internet]. Science. 2015 Apr;348(6232):340–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25837514
41. Carling D. AMPK signalling in health and disease [Internet]. Curr Opin Cell Biol. 2017 Apr;45:31–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28232179
42. Xie Q, Wu Q, Horbinski CM, Flavahan WA, Yang K, Zhou W, et al. Mitochondrial control by DRP1 in brain tumor initiating cells. Nat Neurosci. 2015 Apr;18(4):501–10.
43. Sato A, Sunayama J, Okada M, Watanabe E, Seino S, Shibuya K, et al. Glioma-initiating cell elimination by metformin activation of FOXO3 via AMPK [Internet]. Stem Cells Transl Med. 2012 Nov;1(11):811–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23197693
44. Puscheck EE, Awonuga AO, Yang Y, Jiang Z, Rappolee DA. Molecular Biology of the Stress Response in the Early Embryo and its Stem Cells. Adv Exp Med Biol. 2015;843:77-128. doi: 10.1007/978-1-4939-2480-6_4.
45. Grimes DR, Macauley RJ, Currell F, Scott J, Basanta D. Hypoxia increases the tempo of evolution in the peri-ne-

crotic niche in glioblastoma. bioRxiv. 2018:293712.
46. Yin M, Lu Q, Liu X, Wang T, Liu Y, Chen L. Silencing Drp1 inhibits glioma cells proliferation and invasion by RHOA/ ROCK1 pathway. Biochem Biophys Res Commun. 2016 Sep;478(2):663–8.
47. Lenjisa JL, Tadesse S, Khair NZ, Kumarasiri M, Yu M, Albrecht H, et al. CDK5 in oncology: recent advances and future prospects [Internet]. Future Med Chem. 2017 Oct;9(16):1939–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29076761
48. Brzozowski JS, Skelding KA. The Multi-Functional Calcium/Calmodulin Stimulated Protein Kinase (CaMK) Family: Emerging Targets for Anti-Cancer Therapeutic Intervention [Internet]. Pharmaceuticals (Basel). 2019 Jan;12(1):E8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30621060
49. De Vleeschouwer S, editor. Glioblastoma [Internet]. Codon Publications; 2017. Available from: http://codonpublications.com/index.php/codon/catalog/view/35/133/282-1
50. Joseph JV, Conroy S, Pavlov K, Sontakke P, Tomar T, Eggens-Meijer E, et al. Hypoxia enhances migration and invasion in glioblastoma by promoting a mesenchymal shift mediated by the HIF1α-ZEB1 axis [Internet]. Cancer Lett. 2015 Apr;359(1):107–16. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0304383515000312
51. Wan YY, Zhang JF, Yang ZJ, Jiang LP, Wei YF, Lai QN, et al. Involvement of Drp1 in hypoxia-induced migration of human glioblastoma U251 cells [Internet]. Oncol Rep. 2014 Aug;32(2):619–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24899388
52. Small JV, Stradal T, Vignal E, Rottner K. The lamellipodium: where motility begins [Internet]. Trends Cell Biol. 2002 Mar;12(3):112–20. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0962892401022371
53. Jung JU, Ravi S, Lee DW, McFadden K, Kamradt ML, Toussaint LG, et al. NIK/MAP3K14 Regulates Mitochondrial Dynamics and Trafficking to Promote Cell Invasion [Internet]. Curr Biol. 2016 Dec;26(24):3288–302. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27889261
54. Huang Y, Lin D, Taniguchi CM. Hypoxia inducible factor (HIF) in the tumor microenvironment: friend or foe? [Internet]. Sci China Life Sci. 2017 Oct;60(10):1114–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29039125
55. Bristow RG, Hill RP. Hypoxia and metabolism. Hypoxia, DNA repair and genetic instability [Internet]. Nat Rev Cancer. 2008 Mar;8(3):180–92. Available from: http://www.nature.com/articles/nrc2344
56. Wan YY, Zhang JF, Yang ZJ, Jiang LP, Wei YF, Lai QN, et al. Involvement of Drp1 in hypoxia-induced migration of human glioblastoma U251 cells. Oncol Rep. 2014 Aug;32(2):619–26.
57. Gao X, Mi Y, Guo N, Hu Z, Hu F, Liu D, et al. Disrupted in schizophrenia 1 (DISC1) inhibits glioblastoma development by regulating mitochondria dynamics [Internet]. Oncotarget. 2016 Dec;7(52):85963–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27852062
58. Norkett R, Modi S, Kittler JT. Mitochondrial roles of the psychiatric disease risk factor DISC1 [Internet]. Schizophr Res. 2017 Sep;187:47–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28087269
59. Gao X, Mi Y, Guo N, Hu Z, Hu F, Liu D, et al. Disrupted in schizophrenia 1 (DISC1) inhibits glioblastoma development by regulating mitochondria dynamics. Oncotarget. 2016 Dec;7(52):85963–74.
60. Cildir G, Low KC, Tergaonkar V. Noncanonical NF-κB Signaling in Health and Disease [Internet]. Trends Mol Med. 2016 May;22(5):414–29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27068135
61. Nemoto S, DiDonato JA, Lin A. Coordinate regulation of IkappaB kinases by mitogen-activated protein kinase kinase kinase 1 and NF-kappaB-inducing kinase [Internet]. Mol Cell Biol. 1998 Dec;18(12):7336–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9819420
62. Li Q, Engelhardt JF. Interleukin-1β induction of NFkappaB is partially regulated by H2O2-mediated activation of NFkappaB-inducing kinase. J Biol Chem. 2006 Jan;281(3):1495–505.
63. Smith KA, Waypa GB, Schumacker PT. Redox signaling during hypoxia in mammalian cells [Internet]. Redox Biol. 2017 Oct;13(May):228–34.
64. Wu J, Liu Y, Cho K, Dong X, Teng L, Han D, et al. Downregulation of TRAP1 sensitizes glioblastoma cells to temozolomide chemotherapy through regulating metabolic reprogramming. Neuroreport. 2016 Feb;27(3):136–44.
65. Takamura H, Koyama Y, Matsuzaki S, et al. TRAP1 controls mitochondrial fusion/fission balance through Drp1 and Mff expression. PLoS One. 2012;7(12):e51912. doi:10.1371/journal.pone.0051912.
66. Xiang F, Huang YS, Shi XH, Zhang Q. Mitochondrial chaperone tumour necrosis factor receptor-associated protein 1 protects cardiomyocytes from hypoxic injury by regulating mitochondrial permeability transition pore opening [Internet]. FEBS J. 2010 Apr;277(8):1929–38. Available from: http://doi.wiley.com/10.1111/j.1742-4658.2010.07615.x
67. Matsuoka T, Yashiro M. Rho/ROCK signaling in motility and metastasis of gastric cancer [Internet]. World J Gastroenterol. 2014 Oct;20(38):13756–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25320513
68. Liu L, Luo Y, Chen L, Shen T, Xu B, Chen W, et al. Rapamycin inhibits cytoskeleton reorganization and cell motility by suppressing RhoA expression and activity [Internet]. J Biol Chem. 2010 Dec;285(49):38362–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20937815
69. Aquilanti E, Miller J, Santagata S, Cahill DP, Brastianos PK. Updates in prognostic markers for gliomas. Neuro Oncol [Internet]. 2018 Nov 9;20(suppl 7):vii17-vii26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30412261
70. Turkalp Z, Karamchandani J, Das S. IDH mutation in glioma: new insights and promises for the future [Internet]. JAMA Neurol. 2014 Oct;71(10):1319–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25155243
71. Robert SM, Sontheimer H. Glutamate transporters in the biology of malignant gliomas. Cell Mol Life Sci. 2014 May;71(10):1839–54.
72. Turkalp Z, Karamchandani J, Das S. IDH mutation in glioma: new insights and promises for the future. JAMA Neurol. 2014 Oct;71(10):1319–25.
73. Kong BH, Park NR, Shim JK, Kim BK, Shin HJ, Lee JH, et al. Isolation of glioma cancer stem cells in relation to

histological grades in glioma specimens [Internet]. Childs Nerv Syst. 2013 Feb;29(2):217–29. Available from: http://link.springer.com/10.1007/s00381-012-1964-9
74. Suzuki K, Kawataki T, Endo K, Miyazawa K, Kinouchi H, Saitoh M. Expression of ZEBs in gliomas is associated with invasive properties and histopathological grade. Oncol Lett [Internet]. 2018; 16(2):1758-1764. Available from: http://www.spandidos-publications.com/10.3892/ol.2018.8852
75. Li B, McCrudden CM, Yuen HF, Xi X, Lyu P, Chan KW, et al. CD133 in brain tumor: the prognostic factor [Internet]. Oncotarget. 2017 Feb;8(7):11144–59. Available from: http://www.oncotarget.com/fulltext/14406
76. Roos A, Ding Z, Loftus JC, Tran NL. Molecular and Microenvironmental Determinants of Glioma Stem-Like Cell Survival and Invasion [Internet]. Front Oncol. 2017 Jun;7:120. Available from: http://journal.frontiersin.org/article/10.3389/fonc.2017.00120/full
77. Jackson C, Westphal M, Quiñones-Hinojosa A. Complications of glioma surgery. Handb Clin Neurol. 2016;134:201-18. doi: 10.1016/B978-0-12-802997-8.00012-8.
78. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas [Internet]. N Engl J Med. 2009 Feb;360(8):765–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19228619
79. Schrader M, Bonekamp NA, Islinger M. Fission and proliferation of peroxisomes [Internet]. Biochim Biophys Acta. 2012 Sep;1822(9):1343–57.
80. Dahabieh MS, Di Pietro E, Jangal M, Goncalves C, Witcher M, Braverman NE, et al. Peroxisomes and cancer: the role of a metabolic specialist in a disease of aberrant metabolism [Internet]. Biochim Biophys Acta Rev Cancer. 2018 Aug;1870(1):103–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0304419X18300532
81. Saho S, Satoh H, Kondo E, Inoue Y, Yamauchi A, Murata H, et al. Active Secretion of Dimerized S100A11 Induced by the Peroxisome in Mesothelioma Cells [Internet]. Cancer Microenviron. 2016 Dec;9(2-3):93–105.
82. Cipolla CM, Lodhi IJ. Peroxisomal Dysfunction in Age-Related Diseases [Internet]. Trends Endocrinol Metab. 2017 Apr;28(4):297–308. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1043276016301722