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Parkin and its molecular associations in gliomas – a systematic review

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Abstract

Parkin, a protein encoded by *PRKN,* discovered in the context of Parkinson's disease, controls proteasomal degradation by protein ubiquitination and acts on cell cycle control and mitochondrial homeostasis, among other cellular processes. Parkin has been also implicated in several carcinomas, melanoma and leukemia. In the neoplastic setting, reduced parkin level usually indicates poorer prognosis. Some authors have described the associations between parkin and gliomas. Gliomas are a heterogeneous group of tumors that arise in the central nervous system, astrocytomas being the most common. The aim of this systematic review is to evaluate how parkin behaves in gliomas and the molecular pathways associated in this interaction. A search was conducted in PubMed, EBSCO and Scopus and 8 published articles were identified as eligible studies. The studies were categorized in three groups, according to their main emphasis: *PRKN* mutation patterns detected in gliomas, parkin effects on tumor growth and survival rates, and molecular interactions between parkin and other proteins. The studies showed higher *PRKN* mutation rates and lower parkin expression in high grade gliomas. Patients with higher parkin expression had better overall survival. Besides, different molecular pathways associated with parkin were described, some of them regarded as potential therapeutic targets.

Keywords: Parkin, *PRKN*, Gliomas, GBM, Systematic reviews

Introduction

Parkin is a protein encoded by the *parkin RBR E3 ubiquitin protein ligase* (*PRKN*), a gene discovered two decades ago (Hattori and Mizuno 2017). Back then, it was linked to juvenile Parkinson's disease, which explains the given name "parkin" (Shimura et al. 2000), and over time, the knowledge about parkin has increased substantially. Full-length parkin exhibits 2960 BP, equivalent to 465 amino acids (Kitada et al. 1998). In human brain tissue, parkin is expressed in the cytoplasm and nucleus of neurons and glia cells (Shimura et al. 1999; Yin et al. 2009). D'Agata et al. (2002) analyzed rat brain tissue and concluded that parkin is expressed throughout the brain. However, both in human and other mammals, the primary transcript suffers subsequent alternative splicing, which generates diverse mature RNA and therefore different protein isoforms, as demonstrated by Scuderi et al. (2014). These isoforms differ not only in structure but also in function, and they are expressed differently according to the tissue (Scuderi et al. 2014). D'Amico et al. (2016) showed that some parkin isoforms are expressed globally in rat brain samples while other isoforms differ according to the anatomic region. Parkin classical function is to control proteasomal degradation by inducing ubiquitination of damaged proteins (Martinez et al. 2017; Panicker et al. 2017; Zheng and Hunter 2015) and thus, parkin has a multifunctional role, involved in several cellular processes, such as cell cycle control; cell proliferation and migration; protection against oxidative stress; mitochondrial homeostasis;

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xenophagy; and tumor suppression (Drake et al. 2017; Shires et al. 2017; Durcan and Fon 2015; Gong et al. 2017). Moreover, *PRKN* mutations have been associated with several cancers, such as ovarian, colorectal, liver, melanoma and leukemia, among others (Cesari et al. 2003; Klimczak et al. 2016; Tay et al. 2010; Xu et al. 2014). Reduced parkin levels often indicate an increased risk of lymph node metastasis and increased mortality rates (Da Silva-Camargo et al. 2018). To date, it is still unclear whether these functions are carried out by one protein or different isoforms (Scuderi et al. 2014). Some authors have studied the role of parkin in human gliomas (Yeo et al. 2012; Lin et al. 2015). Maugeri et al. described (Maugeri et al. 2015) 21 parkin isoforms and demonstrated that three variants were found in all human glioblastoma (GBM) samples and GBM-derived cell culture, which could turn these variants into efficient prognostic tools .

The glioma category consists of a group of tumors in which astrocytomas are the most common. Oligodendrogliomas e ependymomas are less frequent gliomas (Ostrom et al. 2017). They are graded by the World Health Organization (WHO) according to their microscopic findings and molecular profile, and high-grade gliomas, including GBM, have poor prognosis and high mortality rates (Louis et al. 2016). Results showed that parkin expression decreases in gliomas, compared to normal brain tissue (Yeo et al. 2012; Mulholland et al. 2006; Yin et al. 2009). Also, parkin expression and tumor grade are inversely correlated, suggesting a loss of *PRKN* function along with tumor progression (Lin et al. 2015; Viotti et al. 2014). The same happens between parkin and p53, in different gliomas, such as GBM and oligodendrogliomas (Viotti et al. 2014). Regarding survival rates, patients with higher parkin levels have better outcome (Yeo et al. 2012; Lin et al. 2015). The present systematic review aims to group these studies involving parkin and gliomas, as well as evaluate the molecular associations described in this interaction.

Methods

Focused question

According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses. (PRISMA) guidelines, a Population, Intervention, Comparison and Outcomes (PICO) question was developed. This is a strategy used in evidence-based practice, that helps to create the research question, as well as the main elements for the literature search (Methley et al. 2014). The final question was: "How does parkin behave in gliomas and what are its associated molecular pathways?"

Literature search

A search was conducted in three different databases: PubMed, EBSCO and Scopus, on November 5th, 2019. The following keywords were used: "PARK2" or "PRKN" or "Parkin", in the fields Title and/or Abstract. *PARK2* and *PRKN* are different names used for the gene that encodes parkin, the latter is the current name. We decided not to include terms related to gliomas, because when those keywords were added, the search showed at times zero results. Therefore, we searched each and every study involving the protein parkin or its gene (*PRKN*; *PARK2*) and selected the ones related to gliomas after reading title and abstract. No publication date or language restrictions were applied.

Registration in PROSPERO

According to recommendations, this review protocol was prospectively registered in PROSPERO – International Prospective Register of Systematic Reviews, and approved on April 27th, 2020, under the number CRD42020172043.

Inclusion and exclusion criteria

Every study had to evaluate parkin and at least one associated molecule or gene, in the context of gliomas. We decided to include both in vitro and in vivo studies, since the number studies was limited.

We first excluded studies unrelated to parkin. Then, studies evaluating parkin's role in the context of other diseases, such as Parkinson's Disease, acute myocardial infarction, infections and tumors other than gliomas were excluded. A more detailed flowchart is shown in Fig. 1.

Data collection and items

Two investigators analyzed the eight studies and extracted data separately. The information collected included: names of the authors, year of publication, whether it included patients or not, whether it included in vitro studies or not (if yes: glioma cell lines used, *PRKN* mutations, colony fold change), whether it included in vivo studies (if yes: animal model, size and weight of the tumor, mortality rates and prognosis), other proteins or genes associated with parkin. Eventually, discrepancies were discussed in order to reach consensus. Those cases in which agreement was not achieved, a third investigator were consulted.

Statistical analysis

This systematic review resulted in a descriptive review, due to the methodological heterogeneity of studies: some approached mutational aspects, some in vitro or in vivo molecular interactions. Thus, a meta-analysis was not performed.

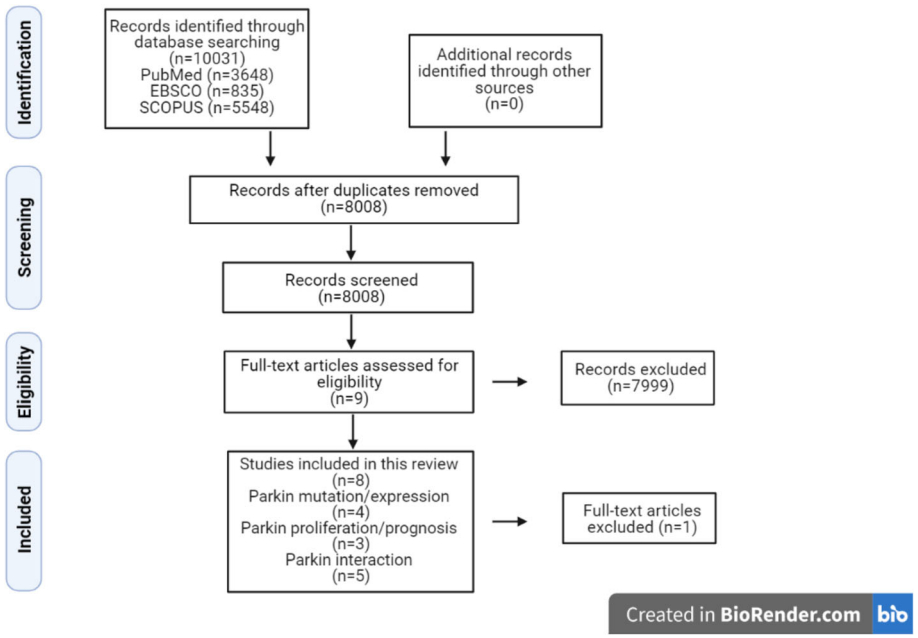

Fig. 1 PRISMA flow diagram, detailing the inclusion and exclusion criteria and the number of studies included and excluded at each step of the literature search

Results

Study selection

Our search was based on title and/or abstract, resulting in 10,031 papers. After excluding 2023 duplicates, we screened title and abstract, and eliminated other 7999 studies, according to inclusion and exclusion criteria described above. Nine studies were thoroughly read, resulting in 8 eligible papers (Fig. 1).

Characteristics of included studies

Among the eight included studies, none of them were randomized clinical trials. Four of them evaluated the mutational patterns in *PRKN* locus and its impact on parkin expression in gliomas. Three of them evaluated correlation between *PRKN* mutations and tumor proliferation status in in vitro models and replicated analysis in in vivo models and/or used public glioma databases. Five studies assessed parkin and other molecular pathways associated.

Main outcome of the studies

We divided the results in three categories. First, we describe *PRKN* mutation patterns in gliomas and the impact on parkin expression. Then, we report how parkin impacts on tumor proliferation and prognosis. Finally, we outline how parkin interacts with other molecular pathways. These findings are summarized in Fig. 2.

PRKN mutation patterns in gliomas

Four studies (Mulholland et al. 2006; Yin et al. 2009; Veeriah et al. 2010 and Yeo et al. 2012) showed the presence of different mutations in *PRKN locus* in gliomas, reducing parkin expression, as well as mutations in other genes in adjacent *loci* (Table 1). Evaluations were based in different techniques such as Fluorescence in situ hybridization (FISH) probes, Deoxyribonucleic acid (DNA) sequencing and comparative genomic hybridization.

Parkin impacts on tumor proliferation and prognosis

Three studies evaluated how parkin expression influences tumor growth using in vitro and in vivo studies (Table 1). In vitro experiments showed that mutated *PRKN* tumor cell colonies had increased growth compared to *wild-type (WT)-PRKN* colonies (Yeo et al. 2012; Lin et al. 2015; Veeriah et al. 2010). These authors showed also higher cyclin level in mutated colonies. In vivo assessments were also performed and showed compatible results to in vitro experiments, since tumor size and weight were inferior in *WT-PRKN* animal models (Yeo et al. 2012; Lin et al. 2015; Veeriah et al. 2010). Also, Yeo et al. (2012) and Lin et al. (2015) found that parkin expression correlates to better prognosis.

Parkin interacts with other molecular pathways

As for parkin associations with other molecular pathways, we have different approaches in five studies. Yeo et al. (2012) evaluated the Phosphatase and tensin

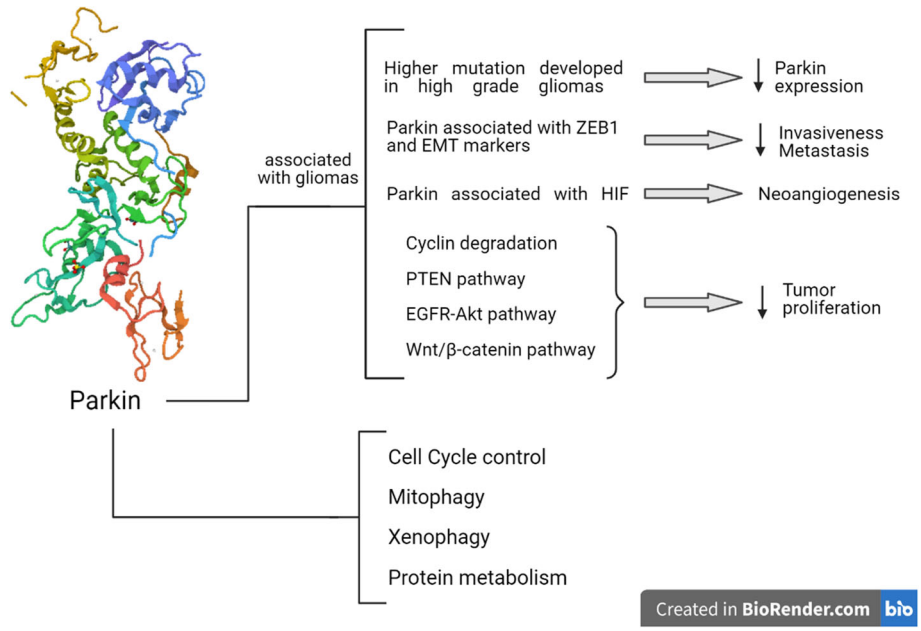

Fig. 2 Parkin molecular interactions and its effects on gliomas

homolog *(PTEN)* pathway, a well-established mutation in high grade gliomas. *PTEN* loss of function promotes abnormal cell proliferation via Phosphoinositide 3-kinases/Protein Kinase B (*PI3K/Akt)* activation. They showed that lower levels of parkin expression resulted in increased *PI3K/Akt* pathway phosphorylation, increasing cyclin expression and inducing more proliferation. Viotti et al. (2014) established an inverse correlation between p53 and parkin expression. Lin et al. (2015) analyzed two molecular pathways and how parkin interacts with them. Through the evaluation of Wnt-beta-catenin pathway, they postulated that parkin induces beta-catenin degradation via proteasome. The second molecular pathway evaluated was Epidermal growth factor receptor-Protein Kinase B (EGFR-Akt). Two studies focused on the fact that GBM is an aggressive neoplasia presenting highly invasive behavior. Maugeri et al. (2016), based upon the fact that GBM presents areas of hypoxia, which induces the expression of hypoxia-inducible factors (HIFs), stimulating pro-angiogenic factors and greater invasiveness, found that parkin suppresses HIFs expression (Maugeri et al. 2016). Wang et al. (2017) also evaluated how parkin influences glioma invasiveness and metastasis (Wang et al. 2017). They demonstrated that parkin downregulates Zinc finger E-box-binding homeobox 1 (ZEB1). This molecule controls epithelial-mesenchymal transition (EMT) markers, such as vimentin and e-caderin and influences tumor invasion. Vimentin expression was higher and e-caderin expression was lower in silenced *PRKN* GBM cells.

Discussion

Parkin is a multifunctional protein discovered in the context of juvenile Parkinson's disease. Lately, this protein has been associated with several types of cancer, including gliomas. Gliomas encompass a heterogenous tumor group classified and graded by the WHO. GBM is the most aggressive high-grade glioma, with poor prognosis and high mortality rates. This systematic review gathered all published studies regarding how parkin behaves in gliomas and evaluated genetic and molecular associations presented in this interaction.

Some studies focused on analyzing mutation patterns *in PRKN,* located in 6q26, and deletions being the most common. Four out of 8 studies described complex genomic alterations in *PRKN locus*. Mulholland et al. (2006) found deletions in 6q25–27, in GBM cell lines and GBM samples affecting not only *PRKN*, but also Insulin-like growth factor 2 receptor (*IGF2R),* Parkin coregulated gene protein *(PACRG)* and Quaking homolog, KH domain RNA binding (*QKI)*. Yin et al. (2009) had similar findings and showed that deletions in long arm of chromosome 6 were observed in about one third of the GBM samples evaluated, impacting on *PRKN, PACRG, QKI* and Phosphodiesterase 10A *(PDE10A).* Veeriah et al. (2010) analyzed GBM samples and detected deletions in 6q chromosome, affecting *PRKN* in 85% of the cases. Yeo et al. (2012) evaluated a public glioma database REMBRANDT (Madhavan et al. 2009) and Freje (Freije et al. 2004) and, like the previous studies, detected several mutations, including loss and gain, in

Table 1 Description of included studies

Author	Year	Cell lines	Evaluation in vitro	Evaluation in vivo	Associated molecules	Association with *PRKN* gene	Type of deletion	Type of mutation	Associated genes	Associated locus
Mulholland et al	2006	U251, U87, U118, CRL1620, CRL2020, CRL2365, CRL2366, CRL2610, CRL2611, Htb138	Protein expression	N/A	TGFβ	Involved in protein degradation as an E3 ubiquitin ligase	Discrete deletion in band 6q25–27	N/A	IGF2R, QKI, PACRG	6q25–27
Yin et al	2009	U87, U118, U138, U343, U373, T98G	Protein expression	N/A	N/A	*PRKN* behaves as a tumor suppressor gene that is inactivated in GBM.	29% of GBM samples showed deletions on the long arm of chromosome 6 and two of these samples had a homozygous deletion (4%) in 6q26–27	N/A	PACRG, QKI, PDE10A	6q25–27
Veeriah et al	2010	T98G, DBTRG, RKO, H441 e H358.	Protein expression and growth of colonies	The wild allele of *PRKN* decreased tumor growth	RING finger domain	*PRKN* mutation and inactivation disrupts the ability of *PRKN* to ubiquitinate cyclin E	Deletions happened in 24.5% of the cases of glioblastoma, being that 90.5% were heterozygous losses	Somatic	Cyclin E	6q26–27
Yeo et al	2012	U87MG, U373MG, U251MG, T98G, HEK293, MCF7	Protein expression and growth of colonies	Overexpressed *PRKN* attenuated the proliferation of glioma	Cyclin-dependent kinase	Parkin negatively influences the cell-cycle program of U87MG cells but through the down-regulation of cyclin D1 instead ofcyclin E expression.	Although the authors did not mention the type of deletion, it occurs at the beginning of transcription	N/A	Cyclin D1 and E, Akt, VEGFR	N/R
Viotti et al	2014	GL15, 42MG, 8MG, SH-SY5Y, MCF7	RNAm, Protein expression	p53 loss of function- associated downregulation of parkin mRNA and protein levels	*p53*	*PRKN* is in quantity inversely proportional to p53 expression and tumor grade	They have found 4 out of 54 samples displaying an allele deletion and all other samples were wild-type *PRKN*	Constitutional mutations (polymorphism) being exons 7 and 5.	TP53, BCL2	N/R
Lin et al	2015	U87MG, U138MG, U251MG, U343MG, A172, T98G	Protein expression and growth of colonies	*PRKN* decreased glioma tumorgenicity	siRNA e shRNA	*PRKN* overexpressed cells had less beta-catenin. When *PRKN* was silenced by siRNA and shRNA, there was an increase in the number of cell colonies	High-amplitude deletion	Somatic	Wnt-betacatenin pathway, EGFR-Akt pathway	N/R
Maugeri et al	2016	U87, T98G	Protein expression	Parkin has been demonstrated to display tumor suppressor activity in cancer. Its expression mitigates the proliferation rate of glioma cells, reduces levels of VEGF receptor 2 (VEGFR2), pro- moting	HIF1, HIF3, VEGFR2	Parkin is expressed when there is hypoxia, regulating the expression of HIF.	N/A	N/A	N/A	N/R

Table 1 Description of included studies *(Continued)*

Author	Year	Cell lines	Evaluation in vitro	Evaluation in vivo	Associated molecules	Association with *PRKN* gene	Type of deletion	Type of mutation	Associated genes	Associated locus
				the suppression of tumoral angiogenesis in GBM						
Wang, H et al	2017	U87, U251, U373, A172, LN444	RNAm	N/A	N/A	*PRKN* knockdown promotes the number of metastases increases.	N/A	N/A	ZEB1, EMT	N/R

N/A Not Applicable
N/R Not reported

PRKN locus in chromosome 6, and an inverse correlation between parkin expression and tumor grade.

Viotti et al. (2014) evaluated parkin expression in three different gliomas: oligodendrogliomas, oligoastrocytomas and GBM, and also observed an inverse correlation between parkin and tumor grade. Lin et al. (2015) also evaluated REMBRANDT database (Madhavan et al. 2009) and found that the frequency of deletions in *PRKN* locus was higher in glioblastomas compared to low-grade gliomas, which correlates to a lower parkin expression in high-grade gliomas.

One of the main associations regarding low parkin expression is increased tumor proliferation. Some authors evaluated this impact by measuring the number of colonies in in vitro studies or measuring the tumor (size and weight) using in vivo models (Yeo et al. 2012; Lin et al. 2015; Veeriah et al. 2010). Veeriah et al. (2010) showed that transfecting *WT-PRKN* into *PRKN* negative-GBM cells resulted in the reduction of colony formation. Yeo et al. (2012) also found that GBM cells with *PRKN* restoration increased parkin expression and reduced colony proliferation in agar plate, compared to control group. Lin et al. (2015) had similar findings, as *WT-PRKN* GBM cells had lower number of colonies, when compared to mutated *PRKN*.

Still regarding tumor growth, some authors investigated how parkin interacts with cyclins. Veeriah et al. (2010) showed that cyclin E expression was lower in *WT-PRKN* cells. This happened because there was as interaction between parkin and cyclin E, followed by cyclin degradation. When they knocked out *PRKN* in these cells, cyclin E expression increased. Yeo et al. (2012) and Lin et al. (2015) had the same response regarding cyclin D1, but not cyclin E.

In vivo assessments were also performed and showed compatible results to in vitro experiments. Veeriah et al. (2010) injected GBM cell line either having *WT* or mutated *PRKN* in murine. Most animals injected with *PRKN* mutations developed tumors, whereas the same happened in only 20% of the animals injected with *WT-PRKN*. As for tumor size, it was greater in mutated *PRKN* animals. Yeo et al. (2012) had the same results, showing greater tumor size and weight in the mutated *PRKN* group. Lin et al. (2015) also showed smaller volume in the mutated *PRKN* group, compared to control. These findings in in vivo studies correlate *PRKN* mutation with reduced tumor burden, which may indicate a tumor suppression function.

Survival rates were also assessed by these authors. Lin et al. (2015) had an extra group of mice followed up and detected higher mortality rates in control group. Therefore, functional *PRKN* tumors were smaller, and animals had better survival rates. Yeo et al. (2012) analyzed parkin expression in REMBRANDT and Freje public glioma databases (Madhavan et al. 2009; Freije et al. 2004) and results showed that higher parkin expression indicated better prognosis. Considering the role played by parkin in protein degradation, these findings suggest that absent or decreased parkin expression results in less cyclin degradation and, therefore, cell cycle progression. It is known that cyclin expression is increased in many tumors. Maybe the reason behind it in gliomas is *PRKN* mutation and less cyclin degradation.

As for parkin associations with other molecular pathways, we have different approaches by the authors. Yeo et al. (2012) evaluated *PTEN* pathway. Low parkin expression resulted in Akt phosphorylation, which increased cyclin D1. Molecules involved in Akt phosphorylation, such as mechanistic target of rapamycin (mTOR), Rapamycin-insensitive companion of mammalian target of rapamycin (Rictor), and Linsidomine (Sin1) as well as their associated substrates, such as Forkhead box O3 (FoxO3a) and Glycogen synthase kinase 3 beta (GSK3b) also had inverse correlation to parkin expression. The same happened in fibroblast cell lines, showing that it is not specific for glioma cells. Thus, low parkin expression increased indirectly cyclin D1 levels. This study suggests that molecules involved with *PTEN* pathway are associated with proliferation and tumor growth.

Lin et al. (2015) analyzed two different molecular pathways and how parkin interacts with them. The first was Wnt-beta-catenin. Molecules involved in this pathway, such as cyclin D1, c-myc and Transcription factor 4 (TCF4) were downregulated in *WT-PRKN* GBM cells, both in messenger Ribonucleic acid (mRNA) levels and protein expression, compared to control cells. When evaluated in Wnt3A medium, which stimulates the Wnt pathway, *WT-PRKN* cells showed lower levels of Axin-like protein (AXIN2), which is a Wnt target, compared to control cells. Also, parkin expression increased in this medium, indicating a possible feedback between *PRKN* and Wnt-beta-catenin. Beta-catenin levels were also evaluated. In silenced *PRKN*, beta-catenin expression increased, and after *PRKN* restoration, beta-catenin levels reduced. Hence, they postulated that parkin induces beta-catenin degradation via proteasome. The second molecular pathway evaluated by Lin and colleagues was EGFR-Akt. There is also an inverse correlation between parkin and EGFR expression. After silencing *PRKN*, EGFR expression increases. When cell lines were stimulated by EGF, control cells increased EGFR expression. Perhaps, like beta-catenin, parkin induces EGFR degradation. Thus, parkin inhibits tumor growth by acting on Wnt and EGFR pathways. The last two studies (Gong et al. 2017; Cesari et al. 2003)

showed how parkin interacts in different molecular pathways that gain importance with a potential therapeutic target. This search becomes particularly important, since GBM therapy is still a challenge.

Viotti et al. (2014) established a connection between p53 and parkin. It is well known that high grade gliomas harbor Tumor protein p53 (*TP53)* mutations, causing overexpression of p53 protein. They evaluated p53 and parkin expression in gliomas and observed an inverse correlation between parkin and p53, and between parkin and tumor grade. In order to evaluate if p53 overexpressed in high grade gliomas was inactive, they evaluated bax and bcl2 expression: the former is stimulated by p53 and the latter, inhibited. Samples showed reduced bax and increased bcl2 expression, indicating that, even though p53 was expressed, it was not functional. GBM cell lines were evaluated and showed lower mRNA and parkin expression levels. And when *TP53* was restored, parkin expression increased. The same results were observed in vivo. *WT-TP53* and silenced *TP53* glioma cells were injected in mice. Parkin expression and mRNA levels were higher in *WT-TP53*. When knocked out *TP53* was restored, parkin expression increased. These are interesting findings because it could mean that not all high-grade gliomas have low parkin expression due to *PRKN* mutations. Some could present this feature because of *TP53* mutation, which impacts on parkin expression.

Two studies based on the fact that GBM is an aggressive neoplasia with highly invasive behavior. Maugeri et al. (2016) focused on GBM's hypoxic areas, which induce the expression of HIFs, stimulating pro-angiogenic factors and greater invasiveness. Hypoxic situations induce HIF1a/HIF3a expression, which contributes to neoangiogenesis and cell viability. Using GBM cell lines the authors compared parkin expression in normoxic and hypoxic situations. The main result showed that parkin expression was reduced in hypoxic situation. Then they evaluated HIF1a and HIF3a expression, in the presence and absence of parkin, in the context of normoxia and hypoxia. In the presence of normoxia and parkin, the hypoxia-inducible factors present opposite characteristics (low expression for HIF1a and high for HIF3a). After this the *PRKN* gene was silenced, and the expression of the hypoxia-inducible factors was changed (high expression for HIF1a and low for HIF3a). In the context of hypoxia, the presence of parkin was associated with high expression for both factors (HIF1a and HIF3a). After silencing *PRKN*, expression was surprisingly reduced in both proteins. So, they postulated that parkin interferes on HIF3a, so that HIF1a is overexpressed in hypoxic situations. This study showed increased HIF1a in GBM cells expressing parkin in low oxygen situations. Could this mean that in GBMs that do not harbor *PRKN* mutations, HIF1a contributes to a poorer prognosis, since it contributes to neoangiogenesis and cell viability? Future studies may answer this question.

Wang et al. (2017) evaluated how parkin influenced invasiveness and metastasis. This is regarded as the first study associating *PRKN* mutations and tumor invasion and metastasis. Wang et al. induced parkin overexpression in a GBM cell line using lentiviral construction. When parkin normal expressing and overexpressing cells were compared, the latter had less migration and invasion capacity. They also showed that silenced *PRKN* GBM cells, compared to cells with functional gene, had higher migration and invasion rates. Next, they analyzed ZEB1 expression in these two cell lines. It is known that ZEB1 has increased expression in high-grade gliomas. ZEB1 expression was lower in GBM cells overexpressing parkin, compared to silenced *PRKN* cells. Thus, parkin downregulates ZEB1. They also evaluated EMT (epithelial-mesenchymal transition) markers: vimentin and e-caderin. Vimentin expression was lower and e-caderin expression was higher in cells overexpressing parkin, while silenced *PRKN* cells showed the opposite. ZEB1 stimulates these markers because, once these cells had ZEB1 knocked out, e-caderin increased and vimentin decreased, which means parkin controls ZEB1, which impacts on EMT markers.

This systematic review could have some limitations. The number of GBM cell lines available is wide and not all authors used the same cell line. This could have some interference in results since different cell lines have different parkin expression levels, as demonstrated by Maugeri et al. (2015). The number of studies is also limited, and as new studies become available, future systematic reviews may show other molecular associations with greater impact in GBM therapy.

Conclusion

This systematic review showed that the frequency of different mutations in the *PRKN locus* is higher in high-grade gliomas. Parkin expression is inversely correlated with glioma grade. Higher parkin expression and lower proliferation rates were observed in low-grade gliomas. Parkin expression was also associated with better prognosis and outcome. Besides, it interacts with different molecular pathways, which could turn out to be therapy targets in the future. In conclusion, based on these studies, we can infer that parkin acts on reducing cell proliferation, reducing cell migration and invasiveness and improving prognosis, through different pathways.

Abbreviations

PRKN: Parkin RBR E3 ubiquitin protein ligase; WHO: World Health Organization; GBM: Glioblastoma; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PICO: Population, Intervention,

Comparison and Outcomes; FISH: Fluorescence in situ hybridization; DNA: Deoxyribonucleic acid; WT: Wild-type; PTEN: Phosphatase and tensin homolog; PI3K/Akt: Phosphoinositide 3-kinases/Protein Kinase B; EGFR: Epidermal growth factor receptor; HIF: Hypoxia-inducible factor; ZEB1: Zinc finger E-box-binding homeobox 1; EMT: Epitelial-mesenchimal transition; IGF2R: Insulin-like growth factor 2 receptor; PACRG: Parkin coregulated gene protein; QKI: Quaking homolog, KH domain RNA binding; PDE10A: Phosphodiesterase 10A; mTOR: Mechanistic target of rapamycin; Rictor: Rapamycin-insensitive companion of mammalian target of rapamycin; Sin1: Linsidomine; FoxO3a: Forkhead box O3; GSK3b: Glycogen synthase kinase 3 beta; TCF4: Transcription factor 4; mRNA: Messenger Ribonucleic acid; AXIN2: Axin-like protein; TP53: Tumor protein p53

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Authors' contributions
Conceptualization: CMS, LN, RGM; Investigation: EMC, LVB, JVAF, DPA; Methodology: CMS, RGM; Supervision: CMS, LFBT; Writing and review: EMC, LVB, CMS. The author(s) read and approved the final manuscript.

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Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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References
Cesari R, Martin ES, Calin GA, Pentimalli F, Bichi R, McAdams H, Trapasso F, Drusco A, Shimizu M, Masciullo V, d'Andrilli G, Scambia G, Picchio MC, Alder H, Godwin AK, Croce CM (2003) Parkin, a gene implicated in autosomal recessive juvenile parkisonism is a candidate tumor supressor gene on chromossome 6q25-q27. Proc Natl Acad Sci 100(10):5956–5961. https://doi.org/10.1073/pnas.0931262100

D'Agata V et al (2002) Distribution of parkin in the adult rat brain. Prog Neuro-Psychopharmacol Biol Psychiatry 26(3):519–527. https://doi.org/10.1016/S0278-5846(01)00301-3

D'Amico AG, Maugeri G, Reitano R, Cavallaro S, D'Agata V (2016) Proteomic analysis of parkin isoforms expression in different rat brain areas. Protein J 35(5):354–362. https://doi.org/10.1007/s10930-016-9679-5

Da Silva-Camargo CCV et al (2018) Parkin protein expression and its impact on survival with advanced colorectal cancer. Cancer Biol Med 15(1):61–69. https://doi.org/10.20892/j.issn.2095-3941.2017.0136

Drake LE, Springer MZ, Poole LP, Kim CJ, Macleod KF (2017) Expanding perspectives on the significance of mitophagy in cancer. Semin Cancer Biol 47:110–124. https://doi.org/10.1016/j.semcancer.2017.04.008

Durcan TM, Fon EA (2015) The three Ps of mitophagy: Parkin, PINK1, and post-translational modifications. Genes Dev 29(10):989–999. https://doi.org/10.1101/gad.262758.115

Freije WA et al (2004) Gene expression profiling of gliomas strongly predicts survival. Cancer Res 64(18):6503–6510

Gong Y, Schumacher SE, Wu WH, Tang F, Beroukhim R, Chan TA (2017) Pan-cancer analysis links Park2 to BCL-XL-dependent control of apoptosis. Neoplasia 19(2):75–83. https://doi.org/10.1016/j.neo.2016.12.006

Hattori N, Mizuno Y (2017) Twenty years since the discovery of the parkin gene. J Neural Transm 124(9):1037–1054

Kitada T et al (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 9(392):605–608

Klimczak PM et al (2016) Association of a PARK2 germline variant and epithelial ovarian cancer in a southern Brazilian population. Oncology 91(2):101–105. https://doi.org/10.1159/000446657

Lin D et al (2015) Genomic and functional analysis os the E3 ligase PARK2 in glioma. Cancer Res 75(9):1815–1827. https://doi.org/10.1158/0008-5472.CAN-14-1433

Louis DN et al (2016) The 2016 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109

Madhavan S et al (2009) Rembrandt: helping personalized medicine become a reality through integrative translational research. Mol Cancer Res 20(7):157–167

Martinez A, Mayor U, Clague MJ (2017) Multi-story parkin. Oncotarget 8(31): 50327–50328. https://doi.org/10.18632/oncotarget.18318

Maugeri G, D'Amico AG, Reitano R, Saccone S, Federico C, Cavallaro S, D'Agata V (2016) Parkin modulates expression of HIF-1a and HIF-3a during hypoxia in glioblastoma-derived cell lines in vitro. Cell Tissue Res 364(3):465–474. https://doi.org/10.1007/s00441-015-2340-3

Maugeri G et al (2015) Expression profile of parkin isoforms in human gliomas. Int J Oncol 47(4):1282–1292. https://doi.org/10.3892/ijo.2015.3105

Methley AM et al (2014) PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. BMC Health Serv Res 14:579

Mulholland P et al (2006) Genomic profiling identifies discrete deletions associated with translocations in glioblastoma multiforme. Cell Cycle 5(7): 783–791. https://doi.org/10.4161/cc.5.7.2631

Ostrom QT et al (2017) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2010-2014. Neuro-Oncology 19:1–88

Panicker N, Dawson VL, Dawson TM (2017) Activation mechanisms os the E3 ubiquitin ligase parkin. Biochem J 474(18):3075–3086. https://doi.org/10.1042/BCJ20170476

Scuderi S, la Cognata V, Drago F, Cavallaro S, D'Agata V (2014) Alternative splicing generates different parkin protein isoforms: evidences in human, rat and mouse brain. Biomed Res Int 2014:1–14. https://doi.org/10.1155/2014/690796

Shimura H, Hattori N, Kubo SI, Mizuno Y, Asakawa S, Minoshima S, Shimizu N, Iwai K, Chiba T, Tanaka K, Suzuki T (2000) Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nat Genet 25(3):302–305. https://doi.org/10.1038/77060

Shimura H, Hattori N, Kubo SI, Yoshikawa M, Kitada T, Matsumine H, Asakawa S, Minoshima S, Yamamura Y, Shimizu N, Mizuno Y (1999) Immunohistochemical and subcellular localization of Parkin protein: absence of protein in autosomal recessive juvenile parkinsonism patients. Ann Neurol 45(5):668–672. https://doi.org/10.1002/1531-8249(199905)45:5<668::AID-ANA19>3.0.CO;2-Z

Shires SE, Kitsis RN, Gustafsson ÅB (2017) Beyond mitophagy, the diversity and complexity of parkin function. Circ Res 120(8):1234–1236. https://doi.org/10.1161/CIRCRESAHA.116.310179

Tay S et al (2010) Parkin enhances the expression of cyclin-dependent kinade 6 and negatively regulates the proliferation of breast cancer cells. J Biol Chem 285(38):2931–2938

Veeriah S, Morris L, Solit D, Chan TA (2010) The familial Parkinson disease gene PARK2 is a multisite tumor suppressor on chromosome 6q25.2-27 that regulates cyclin E. Cell Cycle 9(8):1451–1452. https://doi.org/10.4161/cc.9.8.11583

Viotti J, Duplan E, Caillava C, Condat J, Goiran T, Giordano C, Marie Y, Idbaih A, Delattre JY, Honnorat J, Checler F, Alves da Costa C (2014) Glioma tumor grade correlates with parkin depletion in mutant p53-linked tumors and results from loss of function of p53 transcriptional activity. Oncogene 33(14): 1764–1775. https://doi.org/10.1038/onc.2013.124

Wang H, Jiang Z, Na M, Ge H, Tang C, Shen H, Lin Z (2017) PARK2 negatively regulates the metastasis and epithelial-mesenchymal transition of

glioblastoma cells via ZEB1. Oncol Lett 14(3):2933–2939. https://doi.org/10.3892/ol.2017.6488
Xu L, Lin DC, Yin D, Koeffler HP (2014) An emerging role of PARK2 in cancer. J Mol Med (Berl) 92(1):31–42. https://doi.org/10.1007/s00109-013-1107-0
Yeo C et al (2012) Parkin pathway activation mitigates glioma cell proliferation and predicts patient survival. Cancer Res 72(10):2543–2553. https://doi.org/10.1158/0008-5472.CAN-11-3060
Yin D, Ogawa S, Kawamata N, Tunici P, Finocchiaro G, Eoli M, Ruckert C, Huynh T, Liu G, Kato M, Sanada M, Jauch A, Dugas M, Black KL, Koeffler HP (2009) High-resolution genomic copy number profiling of glioblastoma multiforme by single nucleotide polymorphism DNA microarray. Mol Cancer Res 7(5):665–677. https://doi.org/10.1158/1541-7786.MCR-08-0270
Zheng X, Hunter T (2015) How phosphoubiquitin activates parkin. Cell Res 25(10):1087–1088. https://doi.org/10.1038/cr.2015.97

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