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Invited review

Crosstalks of GSK3 signaling with the mTOR network and effects on targeted therapy of cancer

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ABSTRACT

The introduction of therapeutics targeting specific tumor-promoting oncogenic or non-oncogenic signaling pathways has revolutionized cancer treatment. Mechanistic (previously mammalian) target of rapamycin (mTOR), a highly conserved Ser/Thr kinase, is a central hub of the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR network, one of the most frequently deregulated signaling pathways in cancer, that makes it an attractive target for therapy. Numerous mTOR inhibitors have progressed to clinical trials and two of them have been officially approved as anticancer therapeutics. However, mTOR-targeting drugs have met with a very limited success in cancer patients. Frequently, the primary impediment to a successful targeted therapy in cancer is drug-resistance, either from the very beginning of the therapy (innate resistance) or after an initial response and upon repeated drug treatment (evasive or acquired resistance). Drug-resistance leads to treatment failure and relapse/progression of the disease. Resistance to mTOR inhibitors depends, among other reasons, on activation/deactivation of several signaling pathways, included those regulated by glycogen synthase kinase-3 (GSK3), a protein that targets a vast number of substrates in its repertoire, thereby orchestrating many processes that include cell proliferation and survival, metabolism, differentiation, and stemness. A detailed knowledge of the rewiring of signaling pathways triggered by exposure to mTOR inhibitors is critical to our understanding of the consequences such perturbations cause in tumors, including the emergence of drug-resistant cells.

Here, we provide the reader with an updated overview of intricate circuitries that connect mTOR and GSK3 and we relate them to the efficacy (or lack of efficacy) of mTOR inhibitors in cancer cells.

1. Introduction

For many decades, the mainstays of anticancer therapy have been surgery, radiation, and chemotherapy. Targeted therapy of cancer has become an exciting field for both the academics and the pharmaceutical industry since the approval of imatinib, a tyrosine kinase inhibitor, for treatment of newly diagnosed chronic myelogenous leukemia (CML) in 2002 [1]. While imatinib and its derivatives have revolutionized the therapy of CML and changed the natural history of the disorder, most of the agents targeting cancer cell signaling pathways have met with an extremely limited success, due to a number of reasons that include drug-resistance of neoplastic cells [2]. Cancer cells can develop drug-resistance due to either intrinsic factors (activation of alternative signaling pathways, gene mutations, epigenetic alterations etc.) or extrinsic factors (hypoxia, pH, hormones/cytokines secreted by the tumor microenvironment) [3]. In particular, the tumor spatial and temporal heterogeneity as well as the mutational load of cancers have been directly associated with the emergence of evasive resistance to targeted therapies [4–6].

The phosphatidylinositol-3 kinase (PI3K)/Akt/mechanistic target of rapamycin (mTOR) signaling network is frequently activated in an aberrant manner in most of human cancers, where it controls many processes essential for tumor growth and survival [7–9]. A large array of small molecule inhibitors of the PI3K/Akt/mTOR signaling pathway have been studied in preclinical models of human cancer, where their proved their efficacy as antineoplastic agents. However, only a few of these inhibitors are currently approved for cancer treatment, as clinical trials of drugs targeting PI3K/Akt/mTOR have usually provided

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disappointing results [10,11]. Indeed, despite exciting preclinical findings, drug-resistance remains a primary hindrance in the clinic. Failure of the PI3K/Akt/mTOR inhibitors to act as effective anticancer molecules in humans is due to several reasons, which may also depend on activation/deactivation of other signaling pathways, including those regulated by glycogen synthase kinase-3 (GSK3). Here, we will discuss the most recent advances in understanding how GSK3 signals crosstalk with mTOR and impact on the efficacy of inhibitors that target mTOR.

2. GSK3

GSK3 is a serine/threonine protein kinase, ubiquitously expressed throughout vertebrates, that is capable of phosphorylating over a hundred of substrates, although only a small fraction of these have been convincingly validated in physiological cell systems [12,13]. GSK3 exists in mammalian cells as GSK3α (51 kDa) and GSK3β (47 kDa) isoforms (or, more correctly, paralogs, as they are homologous proteins derived from different genes), that are both constitutively active. GSK3α and GSK3β are encoded by separate genes (named *GSK3A* and *GSK3B* in humans) located at 19q13.2 and 3q13.3, respectively. The two isoforms share a highly conserved (98%) catalytic domain while differing at both termini [14]. Therefore, their overall homology is about 85%.

GSK3α activity is mainly regulated via phosphorylation at Ser21 (inhibition) and Tyr279 (activation), whereas in GSK3β the corresponding amino acidic residues are Ser9 and Tyr216 [15,16]. The phosphorylated Ser residues of GSK3 act as pseudosubstrates that block the substrate binding site and inhibit the enzyme activity [17]. GSK-inactivating kinases include Akt, 90-kDa ribosomal S6 kinase (p90RSK), 70-kDa ribosomal S6 kinase 1 (p70S6K1), and protein kinase A (PKA) [18]. In contrast, the two tyrosine residues are believed to be autophosphorylated by GSK3 itself, although there are reports showing that other kinases could be involved, including mitogen-activated protein kinase kinase (MEK) 1 [19,20]. Nevertheless, regulation of GSK3 activity could also depend on either intracellular localization or interactions with other proteins [18].

For the purposes of this review, it is important to point out that a fraction of GSK3 localizes to the nucleus of both healthy and cancer cells [21–24]. Consistently, some GSK3 substrates (e.g. c-Myc, Snail [25,26]) are nuclear transcription factors.

Both GSK3 paralogs are detected in most human tissues, however their relative abundance varies depending on the cell type being studied [12,27,28]. Moreover, the two paralogs have specific substrates, hence loss of one paralog cannot be compensated for by the other [18], as also demonstrated by the fact that mice with a homozygous deletion of *Gsk3a* are viable despite defects in neuronal development and metabolism. These mice display improved insulin sensitivity, increased hepatic glycogen accumulation, and diminished adiposity. In contrast, homozygous knockout of G*sk3b* is embryonic-lethal, due to liver apoptosis or a cardiac patterning defect [18]. However, in some cases (Wnt/β-catenin signaling for example) both isozymes play similar roles [29].

As it names implies, GSK3 was originally discovered as the protein kinase that phosphorylates glycogen synthase, i.e. the rate-limiting enzyme in glycogen synthesis [30]. However, it is now clear that GSK3 is critically involved in several signaling pathways that control gene transcription, nutrient sensing, mitochondrial function, autophagy, and apoptosis [28]. GSK3 acts as negative regulator of Wnt/β-catenin, Sonic Hedgehog, tyrosine kinase receptor, and G-protein-coupled receptor signaling networks [14]. As to Wnt/β-catenin signaling, GSK3β is part of an inhibitory degradative multiprotein complex that includes adenomatous polyposis coli (APC), axis inhibition protein 2 (AXIN2), casein kinase 1 (CK1), and β-catenin itself [31].

Importantly, both GSK3 isoforms preferentially phosphorylate substrates that have already been phosphorylated by other protein kinases or “priming kinases”. Priming kinases include CK1, extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (p38MAPK), c-Jun N-terminal kinase (JNK), and 5′-adenosine monophosphate-activated protein kinase (AMPK) [32].

Aberrant regulation of GSK3 activity has been reported in several human disorders, including type 2 diabetes, atherosclerosis, Alzheimer's disease, Parkinson's disease, mood disorders, and cancer [33–35], as well as during aging [36]. Regarding cancer, GSK3 was initially considered as a potential tumor suppressor due to its capacity to phosphorylate pro-oncogenic molecules such as c-Jun [37], β-catenin [38], cyclin D1 [39], and c-Myc [25]. This may be true for some skin [40], oral [41], lung [42], and breast cancers [43]. In particular, the phosphorylation of some GSK3 substrates critically involved in the control of cell proliferation or survival, creates a “phosphodegron” which is recognized by specific E3 ubiquitin ligases resulting in targeting of the phosphorylated proteins for degradation by the proteasome [44].

However, over the last 15 years an ever increasing body of evidence has emerged indicating that GSK3 could act as a positive regulator of neoplastic cell proliferation and survival [28,35]. Indeed, GSK3 regulates cancer cell stemness, invasion, proliferation, survival, metabolism, and treatment-resistance also via its effects on microRNAs expression [45–48]. The tumor promoter role of GSK3 is substantiated by the elevated expression levels of the kinase detected in some types of tumors and/or by the antiproliferative effects of GSK3 inhibitors. The cancer types include colorectal [49], pancreatic [50], renal [51], and ovarian [52] carcinoma, as well as glioblastoma multiforme (GBM, [53]), mixed lineage acute leukemia [54], and CML [55].

Overall, the GSK3 paralog that is mostly involved in cancer (either as tumor suppressor or tumor promoter) is the β one [20]. However, GSK3α plays an important role as tumor promoter in acute leukemia development from myelodysplastic syndrome [56] and as a tumor suppressor in oral cancer [41].

3. PI3K/Akt/mTOR signaling

Phosphatidylinositol 3-kinase (PI3K) is a family of inositol lipid kinases that phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2), thereby converting it to phosphatidylinositol 3,4,5- triphosphate (PIP3). PIP3 generated at the plasma membrane acts as a docking site for both phosphoinositide-dependent kinase 1 (PDK1) and Akt. The interaction between PDK1 and Akt results in Akt being phosphorylated at Thr308 [57]. However, PIP3 is important also for the activation of the mTOR complex 2 (mTORC2) [58], that phosphorylates Akt at Ser473 [59]. Phosphorylated Akt then activates its downstream effector, mechanistic target of rapamycin (mTOR) complex 1 (mTORC1) mainly via tuberous sclerosis 1/2 complex (TSC1/TSC2) and the small GTP-ase Ras-homolog enriched in brain (Rheb) [60]. mTORC1 and mTORC2 control many functions that are of fundamental importance for cancer cell pathophysiology, including mRNA translation, ribosome biogenesis, glycolysis, purine and pyrimidine synthesis, lipid synthesis, autophagy, angiogenesis, cell motility, and cytoskeletal organization [61,62]. GSK3 was the first reported substrate of Akt that exerts an inhibitory phosphorylation by targeting an amino-terminal motif conserved in both GSK3α (Ser21) and GSK3β (Ser9) [63]. GSK3 controls a large, functionally diverse array of downstream substrates, most of which are either degraded or inhibited upon phosphorylation by GSK3 [18]. Therefore, Akt upregulates these targets indirectly via the inhibition of GSK3. These substrates include, among the others, the prosurvival B-cell lymphoma 2 (Bcl-2) family member myeloid cell leukemia 1 (Mcl-1) [64] or transcription factors such c-Myc [65], sterol regulatory element binding protein 1c (SREBP1c) [66], nuclear factor E2-related factor 2 (Nfr2) [67], Hypoxia-inducible transcription factor 1α (Hif-1α) [68], and forkhead/winged helix family k1 (Foxk1) [69]. Several targets of GSK3 are positively involved in the control of neoplastic cell proliferation, survival, and metabolism. Therefore, GSK3 switch-off due to aberrantly activated oncogenic Akt signaling [10]

provides an advantage to cancer cells.

4. GSK3 inhibitors

Being a kinase at the crossroads of numerous cell growth and metabolic signaling networks, GSK3 is an attractive therapeutic target in cancer.

The discovery of lithium as a direct and indirect inhibitor of GSK3-related pathways was a major breakthrough in this field [70]. However, over the years several synthetic GSK3 inhibitors have been disclosed, with most of the drugs being ATP-competitive molecules. Early inhibitors (SB216763, for example) were not selective for GSK3, as they also targeted cyclin-dependent kinases (CDK)s, given that CDKs share 33% amino acid identity with GSK3. Subsequently, more specific and potent drugs, such as AR-A014418, CHIR99021, and the closely related compounds, CHIR98023 and CHIR98014, have been released [71]. Usually, compounds targeting GSK3 inhibit both GSK3α and GSK3β with almost equal potency [71]. Nevertheless, selective inhibitors of GSK3α and GSK3β have been described, such as compound 27 and BRD0705 (that target GSK3α [72,73]) or TWS199 (that targets GSK3β [74]).

In contrast, tideglusib (NP031112) is an oral irreversible, non-competitive GSK3β-selective inhibitor that has been tested in patients with neurological disorders, such as Alzheimer's disease and supranuclear palsy [71].

Although a large number of GSK3 inhibitors have entered clinical trials [75], only a few of these studies have been published. LY2090314, an ATP-competitive intravenous GSK3α/β inhibitor [76], has been tested in a phase II clinical trial in patients with acute myelogenous leukemia (AML). Although the drug displayed an acceptable safety profile, the clinical benefit was extremely limited as monotherapy [77]. It has also been used for treating advanced cancers in combination with Pemetrexed and carboplatin, however the authors did not report any therapeutic benefits [78].

In general, the development of GSK3 inhibitors in cancer patients has traditionally been considered extremely challenging because of the very large number of functionally diverse GSK3 substrates, whose targeting could lead to the potential disruption of cellular processes of vital importance for healthy cells. However, the long-term administration of lithium for treatment of bipolar disorder suggests that GSK3 inhibition may be tolerated and be effective for many years [79]. Also tideglusib and LY2090314 seem to be quite well-tolerated [20].

5. mTOR inhibitors

mTOR was originally discovered as the target of the antibiotic rapamycin [80]. Three classes of mTOR inhibitors have been developed and tested as antineoplastic therapeutics in many preclinical studies and clinical trials. The classes comprise: 1) allosteric mTOR inhibitors, which include rapamycin and its derivatives or rapalogs (RAD001/everolimus, CCI-779/temsirolimus). Rapamycin and rapalogs are considered to be selective mTORC1 inhibitors. However, long-term treatment of cancer cells with this class of drugs frequently leads also to inhibition of mTORC2 [2]. 2) ATP-competitive dual PI3K/mTOR inhibitors that target mTORC1, mTORC2, and PI3K. 3) ATP-competitive mTOR kinase inhibitors (TORKIs) that inhibit both mTORC1 and mTORC2, but spare PI3K (Fig. 1). Of these drugs, only the two rapalogs, everolimus and temsirolimus, have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treatment of some types of refractory/relapsed/advanced cancer [81] (Fig. 2).

6. Crosstalks between GSK3 and mTORC1/mTORC2 signaling

GSK3 and mTORC1 are connected together via intricate and not well-defined circuitries that are only now beginning to be unraveled.

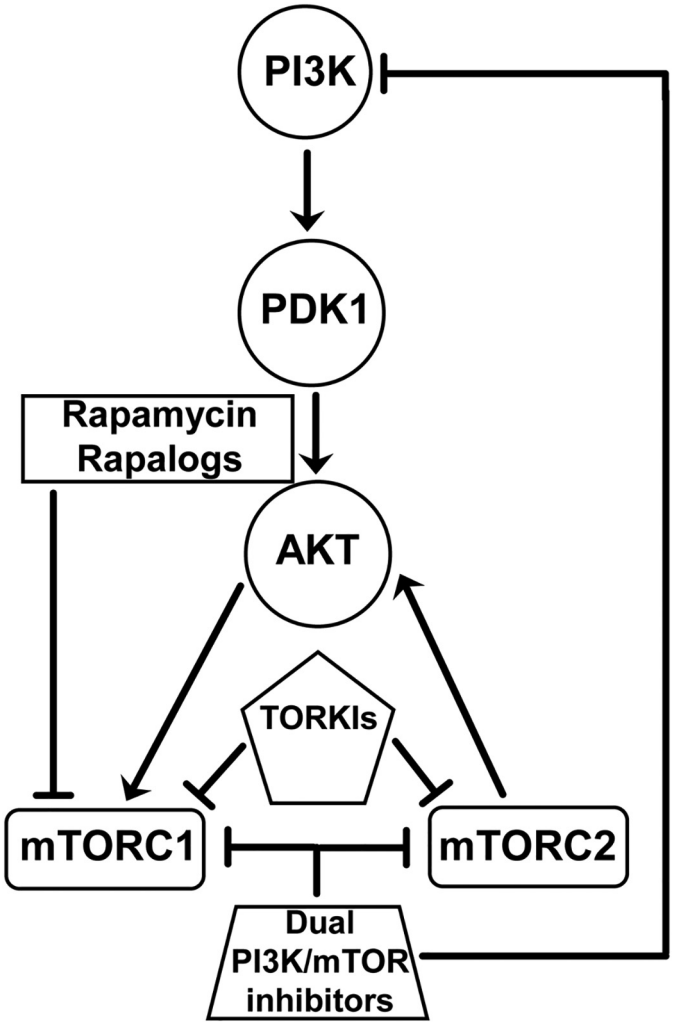

Fig. 1. The three classes of mTOR inhibitors. For the details, see the text. Abbreviations: mTORC1, mechanistic target of rapamycin complex 1; mTORC2, mechanistic target of rapamycin complex 2; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphatidylinositol 3-kinase; TORKIs, mTOR kinase inhibitors.

Evidence indicates the possibility that GSK3 and mTORC1 reciprocally control their activity. Moreover, GSK3 may directly impinge on some mTORC1 downstream targets.

The first report linking GSK3 with mTORC1 demonstrated an inhibition of mTORC1 via phosphorylation of TSC2 by GSK3 at several amino acidic residues (Thr1329, Ser1333, Ser1337, Ser1341), but only when TSC2 had been previously phosphorylated at Ser1345 by AMPK [82]. These findings, obtained in healthy cells (HEK293 cells, murine fibroblasts, bone marrow stromal cells, cementoblasts, etc.), established that Wnt/β-catenin signaling enhanced mTORC1-dependent protein synthesis through the inhibition of GSK3, independently from the transcriptional activity of β-catenin. Furthermore, they supported a model where GSK3 and AMPK depend on each other to negatively regulate mTORC1 activity. Interestingly, an earlier report had documented that GSK3 interacted with TSC2, as demonstrated by co-immunoprecipitation experiments [83]. mTORC1 inhibition via TSC2 phosphorylation by GSK3 was more recently shown to occur also during neural progenitor development [84].

Subsequent studies, that relied on GSK3 pharmacological inhibitors and/or overexpression/genetic downregulation of GKS3 isoforms, came to the conclusion that mTORC1 could be activated by GSK3. However, these studies did not provide mechanisms explaining how GSK3 could actually increase mTORC1 activity [85–88]. Nevertheless, since GSK3

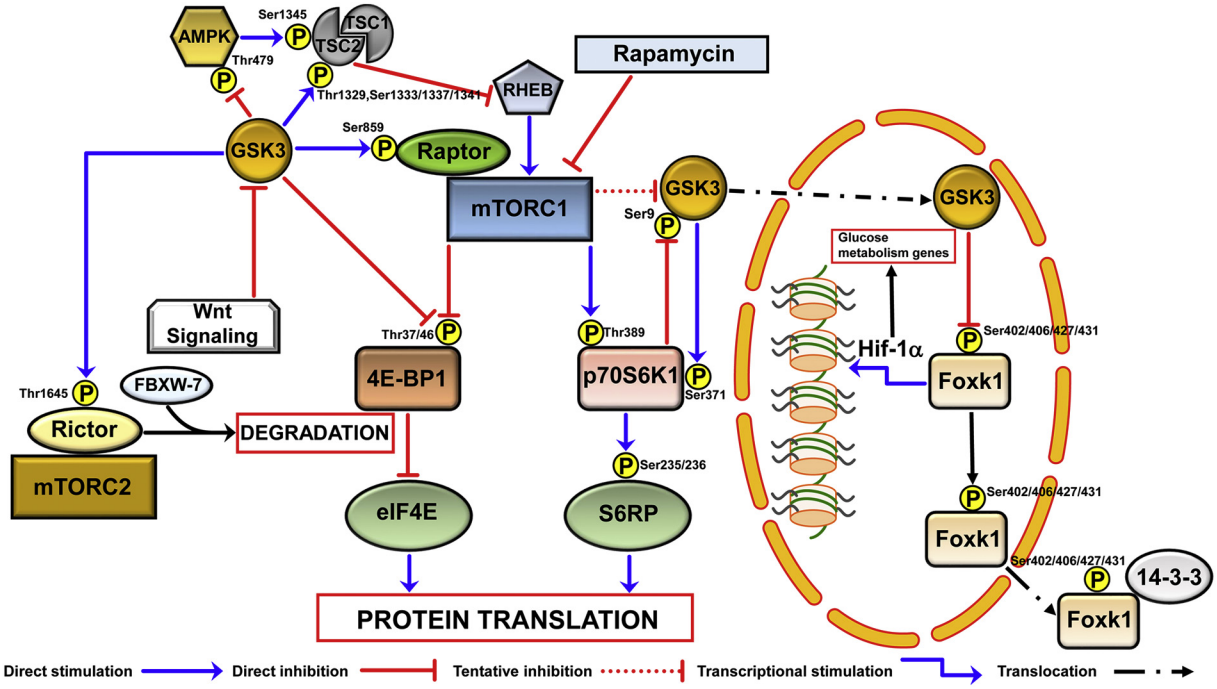

Fig. 2. Circuitries and crosstalks connecting mTORC1 and mTORC2. For the details, see the text. Abbreviations: AMPK, AMP-stimulated protein kinase; 4E-BP1, eIF4E-binding protein; eIF4E, eukaryotic translation initiation factor 4E; FBXW-7, F-box/WD repeat-containing protein 7; Foxk1, forkhead/winged helix family k1; GSK3, glycogen synthase kinase 3; Hif-1α, Hypoxia-inducible factor-1α; p70S6K1, 70-kDa ribosomal S6 kinase 1; Raptor, Regulatory-associated protein of tor; Rictor, Rapamycin-independent companion of tor; Rheb, Ras-homolog enriched in brain; S6RP, S6 ribosomal protein; TSC1, tuberous sclerosis 1; TSC2, tuberous sclerosis 2.

inhibitors did not block phosphorylation of mTORC1 downstream targets in TSC-null cells, it was speculated that GSK3 could act on mTORC1 via TSC1/TSC2, at least in some settings [86]. A possible mechanism linking GKS3 with mTORC1 activation is the GSK3β-dependent phosphorylation of Regulatory-associated protein of tor (Raptor) at Ser859, described by Stretton and coworkers [89]. Raptor is an mTORC1 adaptor protein that presents substrates to the active site of mTOR, because it binds the TOR signaling (TOS) motif characterizing several mTORC1 targets [90]. Either GSK3 pharmacological inhibition or expression of a mutated (S859A) Raptor, loosened the interactions between mTOR and Raptor, thereby leading to dephosphorylation of mTORC1 substrates, such as p70S6K1 (that plays a key role in translation by phosphorylating substrates such as S6 ribosomal protein (S6RP) [91]) and uncoordinated-51-like kinase (ULK1, that is critically involved in autophagy [92]). Importantly, Ser859 Raptor phosphorylation by GSK3 was required for supporting mTORC1-directed amino acid signaling [89]. More recently, a different group reported that either pharmacological inhibition (CHIR-99021, LY2090314) or genetic downregulation of GSK3β in hepatocellular carcinoma (HCC) cells led to an activation of AMPK, thereby decreasing mTORC1 activity and glycolysis, as well as slowing proliferation of cancer cells [93]. These findings imply that GSK3β exerts a stimulatory effect on mTORC1 in HCC cells. Indeed, it is known that GSK3β interacts with the AMPK β regulatory subunit and phosphorylates the AMPK α catalytic subunit at Thr479. This phosphorylation increases the accessibility of the activation loop of the AMPKα subunit to phosphatases, thereby inhibiting kinase activity [94]. Importantly, Fang and coworkers [93] also demonstrated that high levels of GSK3β are an independent negative prognostic factor in HCC patients.

Given these conflicting findings, the role(s) of GSK3 in the regulation of mTORC1 activity might be strictly dependent on the cell type and/or the cell context. Clearly, these are issues of the utmost importance that urgently need further clarification.

On the other side, mTORC1 is capable of inhibiting GSK3α/β by regulating their localization to the nucleus. The occurrence of this phenomenon has been documented in two recently published reports. The first one, that took advantage of human retinal cells and breast cancer cells, evidenced how mTORC1 inhibition by rapamycin treatment led to a partial redistribution of GSK3β from the cytoplasm to the nucleus, thereby ensuing in a reduced expression of both c-Myc and Snail. Consistently, either AMPK activation or amino acid-deprivation (i.e. two conditions that result in mTORC1 inhibition) promoted nuclear translocation of GSK3β [22].

mTORC1 is capable to downmodulate GSK3α activity, thereby resulting in suppressed phosphorylation of the forkhead/winged helix family k1 (Foxk1) transcription factor, a critical mediator of mTORC1-dependent expression of multiple genes associated with glycolysis and downstream anabolic pathways, mainly via the transcriptional upregulation of Hif-1α [69]. It was shown that these events occur through an mTORC1-mediated reduction of nuclear GSK3α signaling, whereas, when mTORC1 is inactivated by rapamycin treatment, Foxk1 is phosphorylated by GSK3α at multiple amino acidic residues (Ser402/406/427/431), binds 14-3-3 proteins, and is excluded from the nucleus. As we shall see in a subsequent subsection, a mechanism that explains how mTORC1 regulates GSK3 subcellular distribution has been disclosed very recently.

Moreover, there is evidence that p70S6K1, a substrate of mTORC1, is capable of phosphorylating GSK3 at Ser9 in both healthy and cancer cells, but only in the absence of TSC1 or TSC2. This aberrant phosphorylation requires amino acids, is inhibited by rapamycin, leads to downregulated GSK3 activity, and contributes to growth-factor independent proliferation of TSC-deficient cells [95]. Furthermore, GSK3 cooperates with mTORC1 by promoting p70S6K1 activity through phosphorylation at Ser371 within the turn motif of p70S6K1, that subsequently increases Thr389 phosphorylation by mTORC1 [96].

Last but not the least, GSK3β directly phosphorylates and inactivates eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1) at Thr37/Thr46, independently of known upstream kinases of 4E-BP1, including mTORC1, thereby upregulating eIF4E-dependent protein synthesis [97,98] similarly to mTORC1.

Regarding mTORC2, GSK3 phosphorylates Rapamycin-insensitive companion of tor (Rictor) at Thr1695. Rictor is a scaffolding component important for mTORC2 assembly, stabilization, and activation [2]. Once phosphorylated by GSK3, Rictor interacts with F-box/WD repeat-containing protein 7 (FBXW-7) that mediates Rictor degradation through ubiquitination/proteasome-dependent mechanism [99]. Therefore, when GSK3 is inactivated by PI3K/Akt signaling, Rictor expression levels and mTORC2 assembly are enhanced, thereby increasing mTORC2 activity. However, a positive effect of GSK3β on mTORC2 activity was reported in mature neurons both in vitro and in vivo, although no molecular mechanisms underlying this stimulation were disclosed [87]. The most important signaling circuitries and crosstalks connecting GSK3 and mTORC1/mTORC2 are summarized in Fig. 1.

7. Influence of GSK3 on the efficacy of mTOR inhibitors

The impact of mTOR inhibitors, including rapalogs, in the clinic has been modest at best, as resistance to these drugs is frequently observed either from the beginning (i.e. innate resistance) or upon long-term treatment (i.e. evasive or acquired resistance). Therefore, in order to improve the antineoplastic efficacy of drugs targeting mTOR, there is an urgent need to further our understanding of the resistance mechanisms [2].

7.1. GSK3 and its impact on rapamycin sensitivity of cancer cells

The first report pointing out the importance of GSK3 in mediating some of the anticancer effects of rapamycin dates back to 2014 when Koo et al. [100] discovered that GSK3 was critically involved in regulating the degradation of some oncogenic proteins and cancer cell sensitivity to rapamycin. Indeed, the basal levels of GSK3 activity positively correlated with the sensitivity of lung cancer cell lines to rapamycin. Consistently, GSK3 pharmacological inhibition antagonized rapamycin cytostatic effects both in vitro and in vivo, while enforced activation of GSK3β sensitized cells to rapamycin. Mechanistically, it was discovered that GSK3 inhibition blocked rapamycin-induced reduction of several oncogenic proteins such as cyclin D1, Mcl-1, and c-Myc, without interfering with the ability of rapamycin to suppress mTORC1 signaling and protein translation. Interestingly, rapamycin induces proteasomal degradation of these oncogenic proteins, as evidenced by their decreased stability induced by rapamycin and rescue of their reduced expression by proteasomal inhibition [100]. These results are in agreement with the findings of Sokolosky et al. [101] who reported a decrease in rapamycin sensitivity when GSK3β activity was inhibited in MCF-7 cells.

More recently, however, J. Blenis group showed that resistance to rapamycin in several cancer cell lines was dependent on expression of Frequently rearranged in advanced T-cell lymphomas protein 1 and 2 (FRAT 1/2) [102]. FRAT 1/2 proteins are well known GSK3-interacting proteins whose function is to export GSK3 from the nucleus [103]. In this context, it is important to emphasize that GSK3β constantly shuttles between the cytoplasm and the nucleus, although it predominantly localizes to the cytoplasm [104]. Of note, GSK3β lacks a canonical leucine-rich nuclear export signal (NES), although its nuclear export is dependent on Chromosomal Maintenance 1 (CRM1), also referred to as Exportin 1. FRAT 1/2 proteins display a NES, interact with GSK3β, and carry it out of the nucleus as part of a protein complex [103]. Even more importantly, FRAT/GSK3β interactions require upregulated PI3K/Akt/mTORC1 signaling, although the exact mechanisms that control these molecular interactions are unclear. Nevertheless, when mTORC1 activity is blocked by rapamycin, GSK3β accumulates in the nucleus where it phosphorylates and inhibits targets important for cancer cell proliferation and metabolism (KAT5 histone acetyltransferase, c-Myc, Foxk1). These findings explain some of the anticancer properties of rapamycin. Consistently, cancer cell lines expressing high levels of FRAT 1/2 are relatively insensitive to rapamycin, whereas downregulation of FRAT 1/2 via siRNA restores rapamycin sensitivity [102]. Interestingly, MCF-7 breast cancer cells express low levels of FRAT 1/2 and are sensitive to rapamycin [102].

In any case, the results by He et al. [102] suggest that FRAT 1/2 expression levels and/or GSK3 subcellular localization might be valuable biomarkers for rapamycin sensitivity, and that targeting FRAT 1/2 expression or their interactions with GSK3 may represent valid therapeutic approaches for overcoming rapamycin resistance.

However, there is also evidence showing that a high expression of GSK3β in the nucleus portends a poorer prognosis in renal cell carcinoma (RCC) [105,106] and in AML patients [23].

Accordingly, either pharmacological inhibition of GSK3β or re-expression of miR-199a (that results in GSK3β downregulation) decreased cancer cell proliferation and survival [105,106]. These data support the concept that in some cancer settings, nuclear localization of GSK3β could favor tumor progression rather than inhibiting it.

Rapamycin resistance has also been linked with the capacity of GSK3 to directly stimulate protein synthesis, thereby bypassing mTORC1. More specifically, it has been demonstrated that GSK3β interacts with and phosphorylates 4E-BP1 at Thr37/46 residues, thereby inactivating 4E-BP1 [97]. This phosphorylation increased eIF4E-dependent protein synthesis in both breast and renal cancer cell lines that were either resistant to rapamycin or that became insensitive after prolonged exposure [97,98]. Accordingly, rapamycin treatment did not block proliferation of resistant cancer cell lines, while a GSK3β inhibitor (AR-A014418) or GSK3β stable knockdown negatively affected both translation and cell proliferation [97]. These findings have led to the hypothesis that GSK3 inhibitors might be combined with rapalogs for a more efficacious treatment of some types of cancer [97].

In general, the findings reported above point out that is some settings GSK3 is required for rapamycin to display its antineoplastic effects, whereas in others GSK3, by bypassing mTORC1 activity, is an important effector of neoplastic cell growth/survival and of resistance to rapamycin.

7.2. GSK3 involvement in resistance to dual PI3K/mTOR inhibitors

GSK3 is a well-known negative mediator of the Wnt/β-catenin signaling cascade. It has been demonstrated that the Wnt/β-catenin/GSK3β axis is involved in resistance to mTOR inhibition in human colorectal carcinoma (CRC) cells. All CRC cell lines that displayed intrinsic resistance to the dual PI3K/mTOR inhibitor PF-05212384 (gedatolisib) harbored a frameshift mutation (c.465_466insC; H155fs*) in T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) 7 (TCF7) [107]. Moreover, resistant cell lines expressed much lower levels of inactive Ser9 p-GSK3β and higher levels of active Tyr216 p-GSK3β when compared with the sensitive cell lines. This difference in the GSK3 phosphorylation pattern could be related to the TCF7 frameshift mutation, as siRNA-mediated knockdown of TCF7 decreased Tyr216 p-GSK3β levels in resistant cells, whereas it increased Ser9 p-GSK3β. However, it is still unknown how the mutation could impact on GSK3β phosphorylation. Interestingly, active GSK3β increased the association of mTOR to Raptor and upregulated mTORC1 activity that was resistant to gedatolisib [107]. Remarkably, these findings are somehow in agreement with the report by Stretton and coworkers on the GSK3-dependent Raptor phosphorylation and enhancement of mTORC1 activity [89].

Moreover, downregulation of GSK3β expression in gedatolisib-resistant cells via siRNA-mediated knockdown or pharmacological GSK3β inhibition by CHIR99021 decreased mTORC1 activity, and rendered the resistant cell lines sensitive to gedatolisib [107]. Therefore, these findings suggest that a combined treatment with a GSK3β inhibitor might be a strategy to overcome intrinsic resistance to PI3K/mTOR-targeted therapeutics in CRC characterized by high levels of active GSK3β.

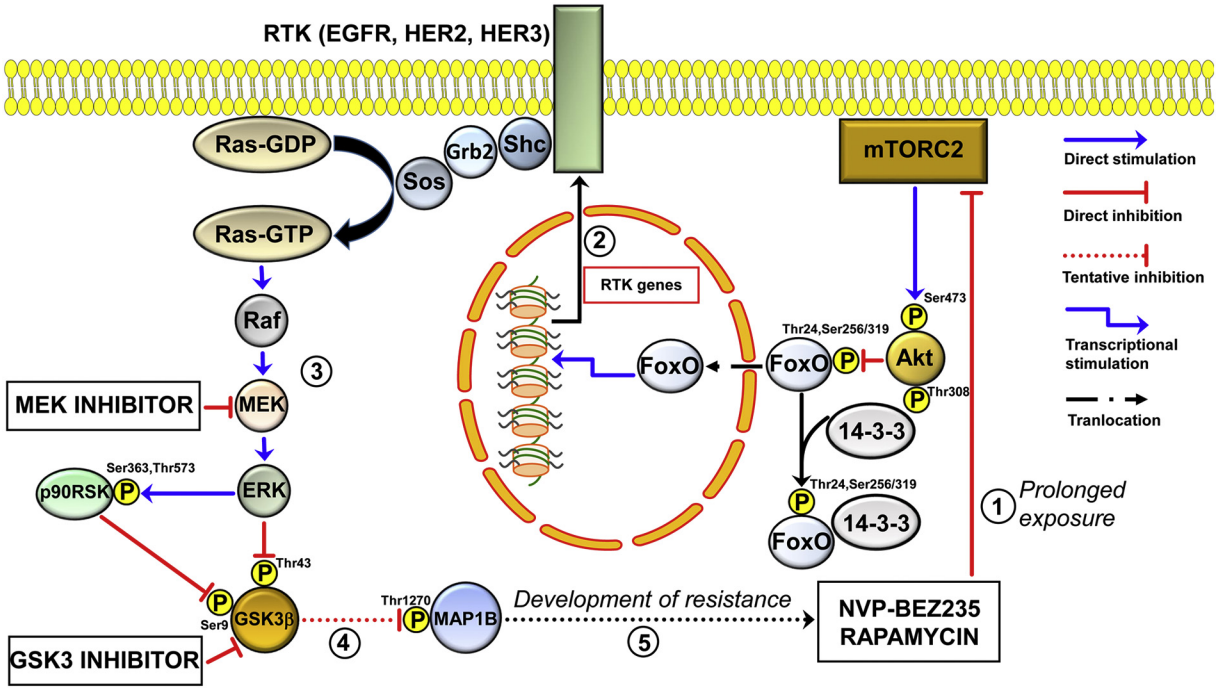

Fig. 3. GSK3β is involved in development of evasive resistance in human glioblastoma cells. Prolonged exposure to mTOR inhibitors (NVP-BEZ235, rapamycin) dampens mTORC2 activity and allows FoxO transcription factors translocation to the nucleus (1); once in the nucleus, FoxO factors upregulate the expression of genes coding for RTK (EGFR, HER2, HER3) (2); enhanced RTK expression/activity increases signaling along the MEK/ERK/p90RSK axis, thereby inhibiting GSK3β (3); as a consequence, the levels of Thr1270 p-MAP1B somehow increase (4) and resistance to mTOR-targeting drugs is induced (5). Abbreviations: EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FoxO, Forkhead box O; Grb2, Growth factor receptor bound protein 2; GSK3β, glycogen synthase kinase 3β; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; MAP1B, microtubule-associated protein 1B; MEK, mitogen-activated protein kinase kinase; mTORC2, mechanistic target of rapamycin complex 2; p90RSK, 90-kDa ribosomal S6 kinase; Ras, Rat sarcoma viral oncogene homolog; RTK, receptor tyrosine kinase; Shc, Src homology 2 domain containing; Sos, Son-of-sevenless homolog;

The involvement of GSK3β in the resistance to the dual PI3K/mTOR inhibitor, NVP-BEZ235, has been documented in human primary GBM cells chronically exposed to this drug [108]. It is worth pointing out that PI3K/Akt/mTOR signaling is frequently altered in GBM [109], however mTOR-targeted therapeutics have failed to improve patient outcome [110].

In this case, however, combined treatment of GBM cells with NVP-BEZ235 and the GSK3β selective inhibitor, CHIR99021, conferred resistance to NVP-BEZ235. Moreover, depletion of GSK3β through shRNA strategy resulted in a marked enhancement of resistance to NVP-BEZ235. In contrast, knockdown of GSK3α had no effects on drug-resistance [108]. Interestingly, Rictor (an mTORC2 component [90]) knockdown by shRNA prevented the development of resistance to NVP-BEZ235, thereby suggesting the involvement of mTORC2. Moreover, the MEK inhibitor AZD6244 decreased resistance to NVP-BEZ235 in vitro and in vivo, indicating the involvement of MEK/ERK signals. A mechanism that might explain this type of resistance is outlined in Fig. 3. It is known that mTORC2 inhibition could lead to MEK/ERK overstimulation via a feedback activation of the Forkhead box O (FoxO) family of transcription factors. In particular, it should be considered that phosphorylation at Ser473 by mTORC2 is required for Akt to exert its inhibitory effects on FoxO proteins nuclear localization [2]. Indeed, FoxO phosphorylation by Akt creates docking sites for 14-3-3 proteins. Once bound to FoxO factors, 14-3-3 proteins enhance FoxO localization to the cytoplasm, thereby blocking their transcriptional activity [111].

When Akt activity is dampened by a prolonged exposure to NVP-BEZ235, FoxO factors could upregulate the expression of a variety of receptor tyrosine kinases (RTKs) [112]. Enhanced RTK expression/activity then leads to activation of the MEK/ERK pathway, as reported by another group [113]. It is still controversial whether ERK could directly phosphorylate GSK3β. However, available evidence indicates that ERK associates with and phosphorylates GSK3β at Thr43, thereby priming GSK3β for subsequent phosphorylation at Ser9 by p90RSK (a downstream target of ERK). These two phosphorylation events result in GSK3β inactivation [114] (Fig. 3).

Importantly, among RTKs whose expression is enhanced via FoxO factors, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (HER) 2, and HER3 play key roles in human GBM cell pathophysiology [115]. Furthermore, the MEK/ERK/p90RSK/GSK3β axis is a common signal, as it was observed in a variety of human tumors, including breast, stomach, kidney, and liver cancer [114].

Laks and coworkers [108] were also able to identify microtubule-associated protein (MAP)1B, as a downstream target of MEK/ERK/p90RSK/GSK3β signaling that led to the development of acquired resistance to NVP-BEZ235 in human GBM cells. Indeed, either GSK3β pharmacological inhibition or depletion of GSK3β via shRNA strategy, decreased the levels of p-MAP1B, a GSK3β substrate. However, GSK3β-dependent phosphorylation had been previously mapped to the Ser1260 and Thr1265 residues of MAP1B [116], while Laks and et al. [108] identified Thr1270 as the hyperphosphorylated residue. Therefore, it could be hypothesized that the enhanced phosphorylation of MAP1B could be due either to the upregulation of a protein kinase or the downregulation of a protein phosphatase that both are controlled via the MEK/ERK/p90RSK/GSK3β axis. Whichever the case, the final result is the appearance of evasive resistance to NVP-BEZ235 (Fig. 3). It is still unknown how MAP1B could determine the development of resistance to this dual PI3K/mTOR inhibitor. It should be considered, however, that MAP1B is involved in several signaling pathways, in addition to its canonical roles in the regulation of actin microfilament and microtubule polymerization [117]. Of note, GSK3β/MAP1B-dependent drug-resistance was also observed in GBM cells treated with rapamycin, consistently with ability of this drug to dampen mTORC2 activity in some cancer settings [108]. These findings are extremely

interesting in that they provide a link between mTORC2 inhibition, MEK/ERK activation, and a GS3Kβ-mediated mechanism of resistance to therapeutics targeting mTOR. Nevertheless, it should be pointed out that activation of GSK3β in GMB correlated inversely with patient outcome as an independent prognostic factor [118]. Therefore, inhibition of GSK3β might well enhance the efficacy of therapeutics targeting mTOR while negatively influencing at the same time other aspects of GBM pathophysiology.

7.3. GSK3 impact on treatment with TORKIs

In general, GSK3 seems to play a dual role also in influencing cancer cell sensitivity to TORKIs.

On one side, Koo et al. [119] demonstrated that GSK3 activity is a critical determinant for TORKIs in vitro efficacy as anticancer therapeutics, as documented via either pharmacologic inhibition or genetic attenuation of GSK3. The negative effects of GSK3 pharmacological inhibition on sensitivity to TORKIs, were observed also in vivo, through the use of human non-small-cell lung carcinoma (NSCLC) xenografted in nude mice. Conversely, expression of a constitutively active form of GSK3β sensitized neoplastic cells to the inhibitors. Of note, higher basal levels of GSK3 activity in a panel of human lung cancer cell lines correlated with more efficacious responses to TORKIs. Mechanistically, it was discovered that TORKIs decreased cyclin D1 expression levels in a GSK3β-dependent manner, independently from their effects on suppressing mTORC1-dependent translation. Indeed, mTORC2 inhibition triggered proteasome-mediated cyclin D1 degradation, that was dampened by silencing expression of F-box protein 4 (FBX4), a component of the S-phase kinase-associated protein 1 (SKP1)-cullin 1-F-box protein (SCF) E3 ligase complex [119,120].

More recently, however, it has been shown that GSK3 could act as the driving force behind the development of evasive resistance to TORKIs [121]. In this respect, it should be considered that both mTORC1 and mTORC2 are involved in regulating glucose, amino acid, lipid, and nucleotide metabolism in cancer cells [122]. Although neoplastic cells usually engage in large scale aerobic glycolysis, as first reported by Otto Warburg in the 1920s [123], it is now equally clear that several types of cancers rely on glutamine catabolism (glutaminolysis) for energy production to satisfy their demand of accelerated proliferation and growth [124]. Glutaminase (GLS) is the enzyme that catalyzes the lysis of glutamine to glutamate. Two isoforms of GLS exist, GLS1 and GLS2 [125]. Importantly, evidence shows that glutaminolysis is associated with the enhanced activity of c-Myc [126], a target of GSK3 signaling. C-Myc-driven cancers are characterized by heightened uptake of nutrients, increased glycolysis and glutaminolysis, as well as by enhanced fatty acid and nucleotide synthesis [127,128]. Moreover, recent evidence indicates that c-Myc-dependent metabolic rewiring of cancer cells allows them to react and adapt to a variety of cues and stresses in their microenvironment [129].

Therefore, a better understanding of the complexity of c-Myc-mediated metabolic reprogramming in tumors as well as how c-Myc cooperates with other metabolic drivers, such as mTORC1 and mTORC2, may provide translational opportunities for cancer therapy using small drug molecules.

Lung squamous cell carcinoma (SCC) is a very aggressive subset of NSCLC, characterized by prognosis poorer than lung adenocarcinoma. Lung SCC cells utilize large amounts of glucose to meet their metabolic needs and display activation of PI3K/Akt/mTOR signaling [130]. Momcilovic and coworkers [121] were able to identify GSK3 as the molecular switch that reprograms tumor metabolism from mTORC1-dependent glycolysis to glutaminolysis in response to prolonged treatment of lung SCC cells with MLN0128 (also known as TAK-228), an investigational-grade TORKI [131].

MLN0128 effectively inhibited mTORC1 activity and suppressed glucose metabolism, however it failed to dampen in vivo tumor growth in a murine model of lung SCC displaying a high dependence on glutamine [121,130]. Using the RH2 human lung SCC line, it was then demonstrated that both MLN0128 and rapamycin suppressed glucose uptake while concomitantly increasing glutamine uptake in vitro. Similar findings were obtained with xenografted RH2 cells. Importantly, it was observed that lung SCC cancers, that were resistant to MLN0128 treatment in mice, had increased levels of Thr308 p-Akt. This phenomenon has been reported in other cancer types, for example in pancreatic carcinoma and AML treated with TORKIs, where it was shown to be dependent on enhanced FoxO/RTK/PI3K/PDK1 signaling [132,133]. High levels of Thr308 p-Akt led to inactivation of GSK3 that resulted in an increased stability of both c-Myc and c-Jun (hyperphosphorylated at Ser73), two proteins critically involved the regulation of GLS1 expression levels. The increase in c-Myc and c-Jun is related to the fact that active GSK3 facilitates the degradation of these oncoproteins via E3 ubiquitin ligases [134,135]. Of note, it was also demonstrated that p-GSK3 levels were a predictive marker of MLN0128 sensitivity in human patient-derived xenografts (PDXs) of lung SCCs, and that the GLS inhibitor CB-839 overcame metabolic reprogramming and resistance to MLN0128 in human lung SCC cell lines and PDXs [121].

Furthermore, Momcilovic and coworkers [121] discovered in human lung SCC, head and neck squamous cell carcinoma, and osteosarcoma a distinctive metabolic signature that predicted outcome and suggested how neoplasias relying primarily on aerobic glycolysis may be responsive to a combinatorial treatment consisting of MLN0128 and CB-839. Such a metabolic signature is defined by a positive staining for glucose transporter 1 (GLUT1), the glutamine transporter solute carrier family 1 member 5 (SLC1A5), p-4EBP1, p-GSK3, and nuclear Ser73 p-c-Jun. Overall, these findings emphasize the relevance of GSK3 and GLS1 as drivers of compensatory glutamine metabolism that results in resistance to TORKIs in some cancer types. They also suggest a rational combination therapy, not based on GSK3 inhibition, that has the potential to overcome resistance to TORKIs.

8. Concluding remarks and future perspectives

Aberrant activation of the PI3K/Akt/mTOR pathway has been observed in multiple cancers. However, the efficacy of FDA- and EMA-approved rapalogs is extremely limited, as drug-resistance has been observed since the beginning of treatment or developed upon prolonged exposure. Resistance has been observed also during clinical trials of dual PI3K/mTOR and TORKIs. Mechanisms of clinical resistance to inhibitors targeting mTOR are unclear [2]. Therefore, understanding and overcoming resistance to mTOR-targeting drugs in neoplastic patients remains a major objective in cancer therapy.

The roles of GSK3 in cancer are paradoxical and enigmatic. This pleiotropic kinase interacts with major multiple signaling networks and for this very reason, it has emerged as a potential target in some human disorders. Aberrant GSK-3 signaling has been implicated in the development and progression of several types of malignant tumors, however therapeutic intervention has been compounded by the fact that GSK3 paralogs can function as either cancer promoters or suppressors based on the cell-type and context.

As summarized in this review, GSK3 and mTORC1/mTORC2 are interconnected by complex, multiple circuitries that have been only recently become to be unraveled. It is evident that, in some cancer settings, GSK3 is a key player involved in the development of resistance to mTOR inhibition. Therefore, from a theoretical point of view, GSK3 inhibitors may be combined with mTOR inhibitors for overcoming drug-resistance. Nevertheless, in other cancer types GSK3 activity seems to be important for mTOR inhibitors to fully unleash their antineoplastic potential, hence the mixed actions of GSK3 make it difficult to harness potential therapeutic interventions. In this case, GSK3 “activators” might be considered, however, at present no specific GSK3 activators are under development [71].

The differences in the roles played by GSK3 in various types of cancer may have hampered the development of GSK3-targeted

therapeutics for antineoplastic therapy. However, further investigation of the mechanisms underlying the opposite actions of GSK3 in different types of tumors, also related to mTOR inhibition, should provide opportunities to better understand the processes controlled by GSK3 and to identify those that may safely benefit from administration of selective drugs. Moreover, this kind of studies could provide insights toward other molecules, controlled by GSK3, that would serve as targets more amenable to a therapeutic intervention, as we have seen in the works of Momcilovic et al. [121] and He et al. [69,102]. These studies could also lead to the development of substrate-competitive GSK3 inhibitors with a high specificity for one of the two paralogs, as already demonstrated in some studies [136–138].

Although the role of GSK3 in tumors is paradoxical, there is substantial evidence to indicate that modulating GSK3 activity is a rational strategy for the treatment of cancer, also for increasing the efficacy of mTOR-targeting agents. Evaluation of the GSK3 expression/phosphorylation profiles, together with the assessment of the activation/inactivation of upstream signaling kinases that regulate GSK3, may be useful biomarkers in selecting patients who can maximally benefit from treatment with GSK3 activity modulators [139].

Last but not the least, a critical step will be to gain a more comprehensive understanding of the reciprocal interactions between GSK3 and mTOR within cells of the tumor microenviroment, including immune and inflammatory cells, as drugs targeting mTOR and GSK3 could have a major impact on them, thereby influencing clinical response [49,140–142].

In conclusion, despite its enigmatic roles, reversing the activation/inactivation status of GSK3, with minimal detrimental effects on healthy cells, appears to be a pragmatic approach to harness this kinase and to improve the efficacy of mTOR inhibitors in cancer patients.

Declaration of competing interest

The authors declare no financial or commercial conflict of interest.

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