Therapeutic Targeting of Cellular Metabolism in Cells with Hyperactive mTORC1: A Paradigm Shift
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Abstract
mTORC1 is an established master regulator of cellular metabolic homeostasis, via multiple mechanisms that include altered glucose and glutamine metabolism, and decreased autophagy. mTORC1 is hyperactive in the human disease tuberous sclerosis complex (TSC), an autosomal dominant disorder caused by germline mutations in the TSC1 or TSC2 gene. In TSC-deficient cells, metabolic wiring is extensively disrupted and rerouted as a consequence of mTORC1 hyperactivation, leading to multiple vulnerabilities, including "addiction" to glutamine, glucose, and autophagy. There is synergy between two rapidly evolving trajectories: elucidating the metabolic vulnerabilities of TSC-associated tumor cells, and the development of therapeutic agents that selectively target cancer-associated metabolic defects. The current review focuses on recent work supporting the targeting of cellular metabolic dysregulation for the treatment of tumors in TSC, with relevance to the many other human neoplasms with mTORC1 hyperactivation. These data expose a fundamental paradox in the therapeutic targeting of tumor cells with hyperactive mTORC1: inhibition of mTORC1 may not represent the optimal therapeutic strategy. Inhibiting mTORC1 "fixes" the metabolic vulnerabilities, results in a cytostatic response, and closes the door to metabolic targeting. In contrast, leaving mTORC1 active allows the metabolic vulnerabilities to be targeted with the potential for a cytotoxic cellular response. The insights provided here suggest that therapeutic strategies for TSC and other tumors with activation of mTORC1 are at the verge of a major paradigm shift, in which optimal clinical responses will be accomplished by targeting mTORC1-associated metabolic vulnerabilities without inhibiting mTORC1 itself. Mol Cancer Res; 13(1); 3–8. ©2014 AACR.

Introduction
Tuberous sclerosis complex (TSC) is an autosomal dominant tumor suppressor gene (TSG) syndrome caused by inactivating germline mutations in the TSC1 or TSC2 gene. Among TSG syndromes, TSC is arguably the most phenotypically and pathologically diverse, with clinical manifestations that impact the central nervous system (seizures, autism, and cognitive impairment), hamartomatous tumors that can begin in fetal life and ultimately involve multiple organ systems (the brain, skin, kidney, heart, and lung), and gender-specific manifestations. The tumors in TSC are pathologically quite distinctive, including subependymal giant cell astrocytomas (SEGA), facial angiofibromas, renal angiomylipomas, and pulmonary lymphangioleiomyomatosis (LAM). Studies initially in Drosophila and later in mammalian cells demonstrated that the TSC protein complex inhibits the mechanistic Target of Rapamycin (mTOR) complex 1 (mTORC1; refs. 1–4). mTORC1 is a master regulator of nutrient and growth factor–induced signaling (3, 5, 6). Pivotal clinical trials of allosteric inhibitors of mTORC1 (Rapalogs) for the treatment of angiomylipomas and SEGAs have revealed tumors partially regress during therapy, and regrow when therapy is discontinued (7–9). In sporadic LAM, which is caused by TSC2 gene mutations (10), lung function tends to stabilize while on sirolimus and then declines when therapy is discontinued (8). These partial clinical responses are consistent with a cytostatic rather than cytotoxic impact on the TSC-deficient tumor cells. Similar results have been observed in clinical trials of Rapalogs for many human malignancies in which complete and durable clinical responses are uncommon. There are two critical caveats to the interpretation of the clinical response of TSC tumors to Rapalogs: first, Rapalogs do not completely repress mTORC1 in most cellular models (11) and second, the TSC proteins are believed to have mTORC1-independent or "non-canonical" effects that may contribute to tumor response during Rapalog therapy (12).

Metabolic Rewiring in TSC-Deficient Cells
It is now evident that cells with hyperactive mTORC1, including TSC-deficient cells, have extensive metabolic rewiring. Over the past decade, the pathways and biochemical mechanisms through which the TSC proteins regulate cellular bioenergetic homeostasis and anabolic metabolism have been elegantly defined and are reviewed elsewhere (3, 5, 13, 14). These defects include a Warburg-like switch to aerobic glycolysis, enhanced glucose flux through the pentose phosphate pathway, glutamine "addiction," and inhibition of autophagy, which limits cell survival particularly under nutrient deprivation conditions (15). These data reveal a fundamental paradox in the pathogenesis of TSC: TSC-deficient cells proliferate excessively, leading to tumors of the brain, skin, heart, kidneys, and lung, yet at the same time, these cells are highly vulnerable to bioenergetic...
Glucose addiction in mTORC1 hyperactive cells

One of the earliest clues to the metabolic defects in mammalian cells deficient in the TSC1 or TSC2 genes arose in 2003 from work by Ken Inoki and Kun-Liang Guan, who discovered that TSC2 protects cells from energy deprivation-induced apoptosis (16). Subsequently, Choo and colleagues (17) found that in the setting of glucose deprivation, TSC-deficient cells had approximately 60% less ATP than control TSC2-expressing cells. mTORC1 inhibition with Rapamycin restored ATP levels in the TSC-deficient cells, thereby preventing energetic stress and cell death in these conditions.

Multiple cellular mechanisms contribute to aberrant glucose metabolism in TSC-deficient cells. It has been recognized for many years that TSC-deficient cells have high levels of HIF1α (18–21), which is regulated at both transcriptional and translational levels by mTORC1. HIF1α induces glycolytic gene expression, enhances glycolysis, and promotes aerobic glycolysis or the “Warburg effect” and is likely to play a central role in the metabolic consequences of TSC deficiency. A transcriptomic analysis of TSC-deficient cells linked TSC-dependent transcription to cellular metabolism including aerobic glycolysis (the Warburg effect) via HIF1α, and the pentose phosphate pathway and fatty acid synthesis via SREBP (22).

Another factor contributing to the glucose metabolic effects of TSC2 deficiency is the regulation of glucose uptake. Both increased glucose consumption (23) and altered localization of the glucose transporter proteins to the cytoplasm instead of the plasma membrane (24) have been reported in Tsc2-deficient cells compared with TSC2-expressing controls. As will be discussed below, glucose uptake is autophagy dependent in Tsc2-deficient cells (15). Additional insights about the metabolic impact of TSC deficiency on glucose homeostasis were reported by Sun and colleagues (23) who found that pyruvate kinase M2 (PKM2) is upregulated in Tsc2-null cells, both in vitro and in vivo, as a consequence of mTORC1 hyperactivation, leading to hypersensitivity of TSC2-deficient cells to the glycolytic inhibitor 3-bromopyruvate in vitro. Other glycolytic enzymes, as illustrated in Fig. 1, may also have roles as therapeutic targets in TSC and mTORC1-dependent diseases. Most recently, the Regulator complex, which serves as a guanine nucleotide exchange factor (GEF) for the RAG GTPases and is essential to amino acid–induced activation of mTORC1 (25), was found to act as a “sensor” under glucose starvation conditions leading to activation of AMPK and recruitment of AMPK to the lysosome (26). This work highlights the intricate connections between mTORC1 and energy sensing programs as well as the critical role of the lysosome in coordinating metabolic homeostatic programs.

Glycolytic rewiring and mitochondrial alterations may contribute to the elevated levels of reactive oxygen species (ROS) that have been identified in many TSC2-deficient cellular models. Recently, a high-throughput screen of more than 6,000 compounds identified chelerythrine, which is best known as a protein kinase C (PKC) inhibitor, as a compound that can selectively induce apoptosis in TSC2-deficient cells via an mTORC1 and ROS-dependent mechanism (27). Chelerythrine provides another critical proof of concept that TSC2-deficient cells can be selectively killed via metabolic mechanisms without the use of an mTORC1 inhibitor.

These findings and others have led to optimism that glucose metabolism can be targeted for the therapy of TSC-associated tumors. It is interesting to note that metabolic targeting has been used for many years in the management of epilepsy in TSC. A “ketogenic diet” that severely restricts glucose intake has been demonstrated to have efficacy in the management of refractory seizures in TSC (28). More recently, a low glycemic index treatment was shown to reduce seizure frequency within 6 months in about 50% of children with TSC, including all 4 children in this study who were younger than 3 years of age (29).

To determine whether inhibiting glucose metabolism could similarly impact tumorigenesis in TSC, Jiang and colleagues (30) used a TSC2-null xenograft model and compared a low-carbohydrate “ketogenic diet” versus a “western diet” versus 2-deoxyglucose. The carbohydrate-free diet was designed to decrease glucose levels and increase ketones. Surprisingly, the mice on the ketogenic diet had markedly enhanced tumor growth, nearly 2-fold greater than the western diet. The molecular mechanisms underlying the unexpected promotion of tumorigenesis remain incompletely understood, and whether this is somehow specific to a xenograft model of TSC versus endogenously arising tumors is not known. This result highlights a key complexity of metabolically targeted therapy for TSC: the neurologic manifestations of TSC may also have a metabolic underpinning and that agents that systemically target mTOR hyperactive tumor

**Figure 1.**
Selected inhibitors of glucose metabolism with potential efficacy in TSC. 3-BrPA, 3-bromopyruvic acid; 2-DG, 2-deoxyglucose; 6-AN, 6-aminonicotinamide.
Glutamine addiction in mTORC1 hyperactive cells

In normal proliferating cells, both glucose and glutamine can feed the Tricarboxylic acid (TCA) cycle. In glutaminolysis, glutamine is converted to alpha-ketoglutarate, which can enter the TCA cycle. Work by Choo and colleagues (17) in 2010 demonstrated that is not necessarily low in all TSC-deficient cells. TTT is an ATPase containing complex that is known to regulate the stability of PI3K-related proteins, including mTOR (34–36). Kim and colleagues discovered that the stability of the TTT–RIVBL1/2 complex is inhibited by glucose or glutamine deprivation, and that TTT–RIVBL1/2 is required for lysosomal localization of mTORC1. The energetic stress which results from the removal of glucose and glutamine leads to a decrease in the interaction between Tel2 and mTOR, along with the TTT components and RIVBL1/2. Most importantly, the lack of these interactions led to the disruption of mTOR’s localization to the lysosome and subsequent activation. This is intriguing because it suggests that inhibition of the energy-dependent functions of the TTT–RIVBL1/2 complex could provide a mechanism for metabolic targeting of cells with hyperactive mTORC1.

More recently, Kim and colleagues (33) have shown that glucose and glutamine positively influence mTORC1 signaling in an AMPK, TSC1/2, and Rag-independent manner. Similarly to Choo and colleagues (17), Kim and colleagues found that withdrawal of both glucose and glutamine strongly decreases mTORC1 activity regardless of AMPK or TSC1/2 status. Interestingly, they identified the Tel2-Tsi1-Tit2 (TTT)–RIVBL1/2 complex in an siRNA screen for genes whose loss blocked mTORC1 signaling in TSC-deficient cells. TTT–RIVBL1/2 is an ATPase containing complex that is known to regulate the stability of PI3K-related proteins, including mTOR (34–36). Kim and colleagues noticed that the stability of the TTT–RIVBL1/2 complex is inhibited by glucose or glutamine deprivation, and that TTT–RIVBL1/2 is required for lysosomal localization of mTORC1. The energetic stress which results from the removal of glucose and glutamine leads to a decrease in the interaction between Tel2 and mTOR, along with the TTT components and RIVBL1/2. Most importantly, the lack of these interactions led to the disruption of mTOR’s localization to the lysosome and subsequent activation. This is intriguing because it suggests that inhibition of the energy-dependent functions of the TTT–RIVBL1/2 complex could provide a mechanism for metabolic targeting of cells with hyperactive mTORC1.

Autophagy addiction in mTORC1 hyperactive cells

It is believed that mTORC1 mainly repressed autophagy via direct phosphorylation of ULK1 (37, 38), although parallel mechanisms are known, including regulation of the ubiquitination and stability of ULK1 via TRAF6 (39). Under nutrient sufficiency, ULK1 activity is downregulated via the phosphorylation of Ser757 by mTORC1 which disrupts the ULK1–AMPK interaction. TSC-deficient tumor cells have low autophagy levels as a consequence of hyperactivation of mTORC1 (40), although in neuronal cells higher levels of AMPK signaling appear to compensate by activating autophagy (41) and thus autophagy is not necessarily low in all TSC-deficient cells. Parkhiko and colleagues (40) found that TSC2-deficient cells are strongly dependent on autophagy for survival. Downregulation of Atg5 causes central necrosis in xenografts of Tsc2-deficient MEFs. This is intriguing because the central areas of tumors are typically the regions experiencing the highest levels of bienergetic stress. In addition, the number and size of tumors in Tsc2−/−/+ mice are decreased by crossing them with Beclin1−/− mice, further supporting the hypothesis that low levels of autophagy represent an Achilles’ heel for TSC2-deficient cells. Thus, TSC2 deficiency results in chronically low levels of autophagy, creating a dependence on autophagy induction for survival under stress conditions. This vulnerability of “autophagy addiction” can be therapeutically targeted by cotreatment with rapamycin and chloroquine. Chloroquine inhibits the final step of autophagy by increasing the pH of the lysosome, which prevents fusion with the autophagosome (see Fig. 3). The combination of chloroquine and rapamycin for 4 weeks inhibits renal tumorigenesis in Tsc2−/−/+ mice and the combination of hydroxychloroquine and sirolimus is currently being tested clinically in a phase 1 clinical trial for LAM, the sirolimus and autophagy inhibition in LAM (SAIL) trial (ClinicalTrials.gov #NCT01687179). Interestingly, treatment with chloroquine alone for 4 months also suppresses tumorigenesis in Tsc2−/−/+ mice (15), suggesting that autophagy inhibition alone could be sufficient to reduce the growth of tumors in TSC.
Inhibition of autophagy with chloroquine leads to increased glucose uptake, increased glucose utilization, and increased levels of pentose phosphate pathway (PPP) intermediates, including ribose-5-phosphate, sedoheptulose-1,7-biphosphate, and fructose-1,6-biphosphate (15). Combined inhibition of autophagy with either chloroquine or Spautin-1 (42) and the PPP with 6-aminonicotinamide, which inhibits glucose-6-phosphate dehydrogenase (G6PD), the rate-limiting enzyme of the PPP, selectively inhibits the growth of TSC2-deficient cells versus TSC2-expressing cells. Interestingly, apoptosis does not appear to be induced in this setting.

It is increasingly clear that autophagy plays a major role in the survival of mTOR hyperactive cells, and other therapeutic strategies to utilize autophagy-dependent mechanisms are emerging. Ng and colleagues (43) recently found that Tsc2-deficient MEFs are hypersensitive to amino acid starvation and hypoxia, which is Atg7 dependent and likely due to the inability of the cells to fully induce autophagy. They found that treatment of Tsc1- or Tsc2-deficient MEFs with 24 hours of low amino acid media or 16 hours of hypoxia leads to a selective increase in cell death of the Tsc1- and Tsc2-deficient MEFs compared with their Tsc1/2-expressing control cells. Downregulation of Atg7 in Tsc2+/− MEFs sensitized them to low amino acid conditions.

Qin and colleagues (44) have shown that ER stress leads to cell death via the induction of autophagy. As expected, they observed that mTOR hyperactive cells are more resistant to ER stress. Their data indicate that the combination of an mTOR inhibitor with an ER stress inducer such as tunicamycin is a potential therapeutic strategy for TSC and other mTOR-dependent diseases. Bray and colleagues (45) have shown that human renal cell carcinomas are resistant to mTOR inhibitors via upregulation of autophagy. Interestingly, the authors show that coinhibition of mTOR and autophagy upregulates RIP kinase activity leading to necroptosis in RCC cell lines in vitro and in xenograft tumors. Wang and colleagues (46) have elucidated a mechanisms through which rapamycin-dependent upregulation of autophagy can be potentiated: activation of CREB1 (which is negatively regulated by autophagy) with forskolin leads to cell death when combined with sirolimus. Xie and colleagues (47) showed that mTOR-dependent melanoma cells can be driven to apoptosis when treated with the mTOR inhibitor temsirolimus and the autophagy inhibitor hydroxychloroquine. Lastly, Alayev and colleagues (48) used the naturally occurring polyphenol Resveratrol in combination with rapamycin to selectively induce death in mTOR hyperactive cells.

In summary, targeting autophagy in the setting of mTOR hyperactivity with either single agents or in combination with mTOR inhibitors appears to be a promising therapeutic avenue for TSC, LAM, and other mTOR-dependent tumors. The SAIL trial for women with LAM is testing the combination of sirolimus and hydroxychloroquine. As discussed earlier, optimal strategies for TSC and LAM may be independent of mTORC1 inhibition. Preclinical data in Tsc2−/− mice support the use of chloroquine alone, although the kinetics are different than sirolimus plus chloroquine, with suppression of tumorigenesis being observed only at longer time points (4 months for chloroquine alone vs. 1 month for sirolimus plus chloroquine). Autophagy inhibitors that are potent and selective would be predicted to be active as single agents in TSC and LAM. In vitro data support the use of autophagy inhibition plus PPP inhibitors to selectively inhibit the growth of TSC2-deficient cells. Several FDA-approved agents have been shown to inhibit the PPP, including imatinib and DHEA.

**Key questions/areas for future research.** TSC and LAM elegantly illustrate how a molecular understanding of pathogenesis can catalyze remarkable clinical progress in rare diseases (49). The
increasing recognition that the metabolism of TSC-deficient cells is extensively rewired provides new opportunities for selective and specific targeting of tumors with mTORC1 hyperactivity. Furthermore, emerging biology clearly connects TSC1/2, mTORC1, and nutrient sensing at the surface of the lysosome (26, 50), recently reviewed by Dunlop and colleagues (51), suggesting that targeting the lysosome will have distinct metabolic consequences in TSC-deficient cells. As these concepts move forward, key questions and unknowns include: (i) What are the best metabolic targets to achieve specificity for TSC-deficient cells? Multiple potentially targetable alterations exist in TSC-deficient cells as a consequence of mTOR activation, including glycolysis, glutaminolysis, and autophagy. Which of these targets would be predicted to have the best therapeutic window to target the metabolic defects in TSC? Ideally, metabolically targeted agents would induce cell death selectively in the TSC-deficient cells, thereby inducing a sustained and durable response; continuous therapy would not be required. (ii) What are the best preclinical models to test metabolic targeting? TSC is a multisystem disease and the metabolic dependencies of TSC-deficient cells are likely to vary based on the tissue type, tumor size and rate of growth, and stromal factors including angiogenesis and lymphangiogenesis. Even within a tumor, there will be metabolic heterogeneity. For example, angiomylipomas contain vascular, smooth muscle, and fat elements, each of which is likely to be metabolically distinct. In LAM, the TSC-deficient LAM cells are outnumbered by stromal cells, accompanied by distinctive lymphangiogenic network. Xenograft models, while providing many advantages in terms of efficiency and cell lineage flexibility, may have altered vasculature leading to biologically divergent dependencies that are not recapitulated by endogenously arising tumors. The Tsc2<sup>+/−</sup> mouse model, which develops renal epithelial cysts and neoplasms, provides an alternative to xenograft models. Notably, autophagy inhibition with chloroquine has been shown to decrease renal tumorigenesis in the Tsc2<sup>+/−</sup> mice (40), whereas Metformin had no effect (52). Proteasome inhibitors, which have in vitro efficacy in some TSC cellular models, also had no effect in the Tsc2<sup>+/−</sup> mice (52). Clearly, many variables need to be carefully considered as in vitro findings are translated into preclinical and clinical studies. (iii) What are the optimal clinical scenarios in which to test metabolically targeted therapeutic strategies in humans with TSC and LAM? To our knowledge, the ongoing "SAIL" trial (sirolimus and autophagy inhibition in LAM, NCT01687179) which is testing the safety of rapamycin/sirolimus plus hydroxychloroquine in LAM represents one of the first initiatives to target the metabolism of TSC-deficient cells in humans. In TSC and LAM, biomarkers that identify the patients most likely to benefit from metabolically targeted therapies and that provide early indicators of therapeutic benefit are urgently needed to streamline clinical trial design.

**Conclusion**

In 2010, Abraham and Eng (53) were among the first to address the balance between the prosurvival and the antitumor effects of mTORC1 inhibition, asking whether the "salutary effects of rapamycin-related mTORC1 inhibitors on metabolic balance under stress conditions actually compromises the antitumor activities of these compounds in the clinical setting." They proposed that "a more complete understanding of the metabolic rewiring that allows them to survive such energy deficits may well reveal some intriguing new targets for cancer drug development."

Four years later, the metabolic rewiring in TSC-deficient cells is further elucidated through elegant work by many laboratories. In aggregate, these data strongly support the fundamental hypothesis that inhibition of mTORC1 creates bioenergetic stability and promotes tumor viability via autophagy and other mechanisms. Most excitingly, recent work has revealed therapeutic strategies that target the metabolism of TSC-deficient cells without the use of mTORC1 inhibitors, exactly as predicted in 2010 by Abraham and Eng. TSC-deficient cells exist on a "metabolic cliff" because of the bioenergetic imbalance created by mTORC1 hyperactivation, creating exquisite sensitivity to further bioenergetic stress, such as glucose deprivation plus glutamine deprivation, or autophagy inhibition. Treatment with an mTORC1 inhibitor relieves this metabolic stress, restoring bioenergetics balance. Therefore, we believe that optimal targeting of TSC-associated tumors as well as the majority of sporadic tumors with hyperactive mTORC1 will be achieved without the use of mTORC1 inhibitors.

In conclusion, mTORC1 hyperactivation generates metabolic vulnerabilities that can be therapeutically targeted, with high specificity for the TSC-deficient cells versus TSC-intact counterparts, and with the potential for selective induction of cell death. In striking contrast, mTORC1 inhibition relieves these metabolic vulnerabilities and induces strong cytotoxic, prosurvival pathways, including the induction of autophagy that result in cell survival, dormancy, and cytostasis. Although Rapalogs generate a cytostatic response, metabolically targeted therapies offer an opportunity for a cytocidal response. We are poised to translate these key findings in preclinical models of TSC and LAM, and to identify optimal agents and strategies for clinical trials. The future of targeting mTORC1 hyperactive tumors may rely primarily on strategies that do not include mTORC1 inhibition, representing a major paradigm shift in an active area of basic and clinical investigation.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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