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Review

Cancer Research

Transcriptional Control of Cellular Metabolism by mTOR Signaling

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Abstract

Tumor cells are characterized by adaptations in cellular metabolism that afford growth and proliferative advantages over normal cells and, thus, contribute to cancer pathophysiology. There is an increasing appreciation of the fact that oncogenic signaling controls the metabolic reprogramming of cancer cells; however, the mechanisms and critical players are only beginning to be elucidated. Recent studies have revealed that mTOR complex 1 (mTORC1), a master regulator of cell growth and proliferation downstream of oncogenic signaling pathways, controls specific aspects of cellular metabolism through the induction of metabolic gene expression. mTORC1 activation is sufficient to promote flux through glycolysis and the oxidative branch of the pentose phosphate pathway, as well as to stimulate *de novo* lipogenesis, all processes that are important in tumor biology. As mTORC1 signaling is aberrantly elevated in the majority of genetic tumor syndromes and sporadic cancers, this pathway is poised to be a major driver of the metabolic conversion of tumor cells. *Cancer Res; 71(8); 2815–20. ©2011 AACR.*

Introduction

Cancer researchers have known for more than 80 years that the metabolic processes at work within tumors are vastly different from those of their tissue of origin (1). This metabolic shift promotes bioenergetic and anabolic changes that provide a growth and proliferation advantage to tumor cells under the suboptimal growth conditions of the tumor microenvironment. This distinction between the behavior of normal and tumor cells, by definition, represents a therapeutic opportunity to selectively target tumor cells. However, there is a substantial void in our knowledge of how oncogenic events alter the metabolic program of cancer cells and how best to take advantage of these differences for the development of specific antitumor therapies. Our laboratory has recently found that the mTOR signaling pathway, which is frequently activated in genetic tumor syndromes and cancers, induces the expression of a metabolic gene regulatory network (2). The potential implications of these findings for tumor cell metabolism, growth, and viability are discussed below.

Toward Understanding the Consequences of Aberrant mTORC1 Signaling

The serine/threonine kinase mTOR exists within 2 distinct protein complexes, and we focus here on mTOR complex 1 (mTORC1), which senses the availability of growth factors, nutrients, and cellular stress to coordinate anabolic processes promoting cell growth and proliferation (3). Most of the signals that regulate mTORC1 are transmitted through upstream signaling pathways that converge upon a small G-protein switch. Rheb is a Ras-related small G protein that, when in its GTP-bound state, is a potent and essential activator of mTORC1. In general, signals impinging on mTORC1 regulation alter the GDP/GTP–bound status of Rheb by regulating the TSC1-TSC2 complex, which has GTPase-activating protein (GAP) activity toward Rheb. Therefore, when the TSC1-TSC2 complex is active, it stimulates the intrinsic GTPase activity of Rheb, effectively converting Rheb to its GDP-bound state and shutting down mTORC1 activity (4). Growth-promoting conditions inhibit the TSC1-TSC2 complex to stimulate mTORC1, whereas poor growth conditions activate the TSC1-TSC2 complex to suppress mTORC1 signaling. The TSC1-TSC2 complex is encoded by the 2 tumor suppressor genes mutated in the genetic tumor syndrome tuberous sclerosis complex (TSC). Importantly, within the network of signaling pathways that regulate mTORC1 activity upstream of the TSC1-TSC2 complex are numerous oncogenes and tumor suppressors, including those most commonly affected in human malignancies (Fig. 1). In fact, aberrant activation of mTORC1 signaling is a frequent occurrence in the most common types of human cancer and a variety of genetic tumor syndromes (5).

Although we have made enormous progress in understanding the upstream signaling pathways that regulate mTORC1, relatively little is known about the downstream consequences of mTORC1 activation. The 2 best-characterized, direct targets of mTORC1 are the ribosomal S6 kinases (S6K1 and S6K2) and eukaryotic initiation factor 4E (eIF4E)–binding proteins (4EBP1 and 4EBP2), which are, respectively, activated and inhibited by mTORC1. Through these targets, and likely

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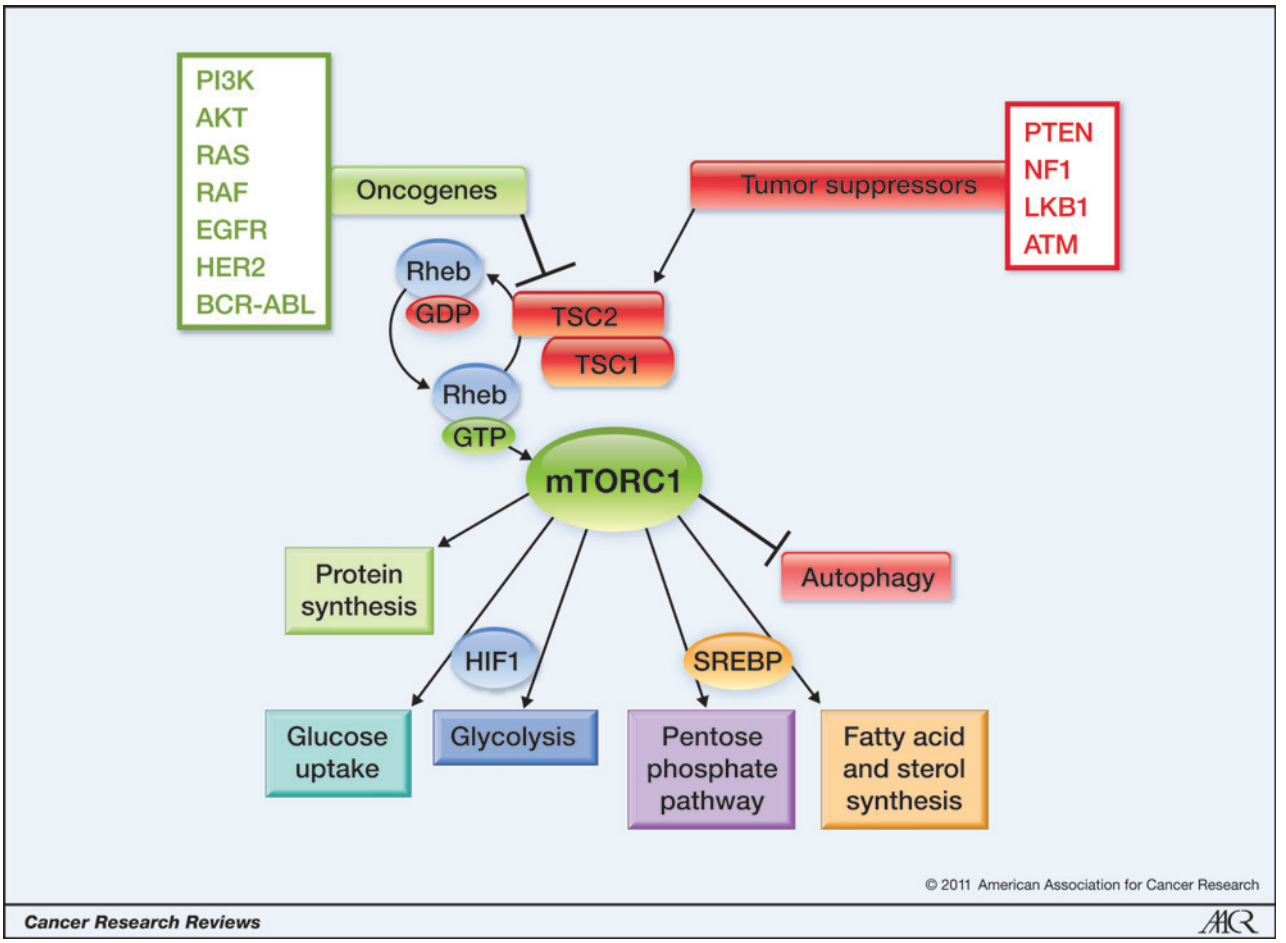

Figure 1. Model of the small G-protein switch controlling mTORC1 activation downstream of common oncogenes and tumor suppressors and the effects on cell physiology. A network of upstream signaling pathways comprised of the oncogenes and tumor suppressors listed control the activation status of mTORC1 by regulating the TSC1-TSC2 complex. Oncogenic signaling events inhibit the TSC1-TSC2 complex to promote the accumulation of Rheb-GTP and subsequent activation of mTORC1. Reciprocally, through their inhibitory effects on oncogenic signaling, tumor suppressors, in effect, stimulate the TSC1-TSC2 complex to inhibit the activation of mTORC1 by Rheb. In addition to its previously defined roles in promoting protein synthesis and blocking autophagy, mTORC1 activation can drive specific metabolic processes through regulation of metabolic gene expression. These processes include glucose uptake and glycolysis through hypoxia-inducible factor 1(HIF1) and the pentose phosphate pathway and lipid biosynthesis through sterol regulatory element binding protein (SREBP; see text for details).

others, mTORC1 regulates specific aspects of cap-dependent translation initiation. In addition, through poorly understood mechanisms, mTORC1 activation promotes ribosome biogenesis, thereby enhancing the protein synthetic capacity of the cell. Through mechanisms that are emerging, but incompletely elucidated, mTORC1 is also a key inhibitor of the catabolic process of autophagy. For more information on these broad subject areas related to mTOR, see reviews from Ma and Blenis (6), Mayer and Grummt (7), and Neufeld (8). Given its common activation in human cancers, there is much interest in elucidating other downstream processes controlled by mTORC1 to better understand its contributions to cancer pathogenesis and to identify novel therapeutic avenues.

To elucidate the cell intrinsic effects of mTORC1 activation, we recently used a reductionist approach to isolate mTORC1 signaling from the many branching pathways lying upstream (2). We took advantage of the fact that loss of TSC1 or TSC2 results in constitutive Rheb-GTP loading and mTORC1 activation, even in the absence of growth factors. Therefore, cell lines lacking TSC1 or TSC2 represent a genetic gain-of-function model, in which mTORC1 activation is uncoupled from regulation by upstream pathways that normally converge upon the TSC1-TSC2 complex. Combining the analysis of these cells with the use of rapamycin, a highly specific pharmacologic inhibitor of mTORC1, provides an approach to identify cellular processes that mTORC1 activation alone is sufficient to regulate.

Transcriptional Control of Metabolic Pathways Downstream of mTORC1

We employed unbiased genomic and metabolomic analyses to identify mTORC1-regulated transcripts and metabolites (2). Gene expression arrays were used to compare *Tsc1*- and *Tsc2*-deficient mouse embryo fibroblasts to their

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littermate-derived wild-type counterparts under serum-free growth conditions, in which mTORC1 is inactive in wild-type cells and fully stimulated in both *Tsc1* and *Tsc2* null cells. A time course of rapamycin treatment was included to establish a role for mTORC1 in any changes detected. Transcripts were classified as being induced by mTORC1 signaling only if they were significantly elevated in both *Tsc1* and *Tsc2* null cells relative to wild-type and reduced toward wild-type levels by rapamycin treatment. Only 130 genes met these highly stringent criteria. Gene set enrichment analysis revealed significant overrepresentation of genes from 3 specific metabolic pathways among those induced by mTORC1 signaling: glycolysis, the pentose phosphate pathway, and lipid and sterol biosynthesis. To determine whether the stimulation of these metabolic genes downstream of mTORC1 altered cellular metabolism, we used both focused metabolic assays and metabolomic approaches. Steady state and metabolic flux analyses revealed that mTORC1 activity promotes flux through glycolysis and, specifically, the NADPH-producing oxidative arm of the pentose phosphate pathway. Finally, we found that *Tsc2*-deficient cells show an mTORC1-dependent increase in *de novo* lipogenesis. Therefore, the robust pathway-specific induction of metabolic genes by mTORC1 signaling drives corresponding metabolic changes in cells.

To gain insight into how mTORC1 controls metabolic gene expression and, thereby, affects cellular metabolism, we used a bioinformatic approach to identify overrepresented transcription factor binding motifs in the promoters of mTORC1-regulated genes (2). Interestingly, the 2 most significantly enriched *cis*-regulatory elements among rapamycin-sensitive genes in this study were for SREBP and Myc, both of which are global regulators of cellular metabolism. Importantly, c-Myc and HIF1 recognize an overlapping motif and are both known to promote the transcription of glycolytic genes (9). We found that, in the setting of TSC gene disruption, mTORC1 signaling drives glucose uptake and glycolysis through upregulation of HIF1α. On the other hand, the SREBPs (SREBP1a, 1c, and 2) are known to stimulate the expression of a large number of lipid and sterol biosynthesis genes (10). We showed that these transcription factors are, indeed, essential for the mTORC1-induced expression of these genes and for the promotion of *de novo* lipogenesis by mTORC1 signaling (2). Interestingly, SREBP1 was also found to be required for the mTORC1-dependent increase in the expression of glucose 6 phosphate dehydrogenase (*G6pd*), encoding the rate-limiting enzyme of the oxidative branch of the pentose phosphate pathway. This finding suggests that mTORC1 can coordinate *de novo* lipogenesis and the generation of reducing equivalents required to fuel this anabolic process through regulation of this transcription factor. Importantly, 2 previous studies showed that activated alleles of Akt, which potently activate mTORC1, can stimulate HIF1α and the SREBPs to respectively induce expression of glycolytic and lipogenic gene sets, similar to those identified in our study (11, 12). These results suggest that activation of mTORC1 through upstream oncogenic pathways will also promote these metabolic changes.

Normoxic Induction of HIF1α by mTORC1

HIF1α protein levels are elevated in many human cancers through genetic events or intratumoral hypoxia, which promote its stability, and increased HIF1α levels correlate poorly with patient survival (13). We find that mTORC1 activation alone is sufficient to drive increases in HIF1α levels under normoxic conditions (2), without effects on its stability (S. Menon and B.D. Manning, unpublished data). Consistent with previous findings (14, 15), we show that, through phosphorylation and inhibition of 4EBP1, mTORC1 can stimulate cap-dependent translation from the 5′-untranslated region of the HIF1α mRNA. However, we also found increases in both HIF1α and HIF2α transcripts, suggesting either additional mechanisms of regulation or auto-regulation of their expression. The ability of mTORC1 to promote elevated normoxic levels of HIF1α suggests that even oxygenated regions of tumors characterized by high mTORC1 activity could display HIF1α-dependent metabolic changes, resulting in aerobic glycolysis (more commonly referred to as the Warburg effect). The ability of mTORC1 to promote glucose uptake and gylcolytic flux through HIF1α also suggests that fluorodeoxyglucose (18F; FDG)–positron emission tomography (PET) positivity may be a useful indicator for monitoring mTOR-driven tumors, a notion supported by genetic tumor models in mice (11, 16). Like HIF1α, c-Myc can also induce the expression of genes involved in glucose uptake and glycolysis (9) and can be translated in an mTORC1-dependent manner in some settings (17). Therefore, it is possible that in such settings, mTORC1 might enhance glycolytic gene expression through c-Myc rather than HIF1α.

SREBP as a Key Effector of mTORC1 Signaling

The data from our study and other recent studies have shown that the SREBPs are major downstream effectors of mTORC1. SREBPs play an important role in both the physiologic and pathologic regulation of lipid metabolism. Because aberrant lipid production can be detrimental to cells and tissues, activation of SREBP is a complex, highly regulated process. SREBPs are synthesized as inactive precursors that reside in the endoplasmic reticulum (ER). Signals that indicate the need to produce lipid, such as insulin or decreased intracellular levels of cholesterol, induce SREBP to traffic to the Golgi, where it is proteolytically processed, releasing the active transcription factor form, which then translocates to the nucleus to turn on target genes (10). Previous studies suggest that SREBP activation is controlled by growth factors through the phosphoinositide 3-kinase (PI3K)–Akt pathway (18, 19). Akt has been proposed to regulate SREBP, in part, by promoting the stability of its processed form through inhibition of glycogen synthase kinase 3 (GSK3), which has been shown to phosphorylate the processed active form of SREBP1 and target it for proteasomal degradation (20). However, consistent with our findings, Akt has been shown to activate SREBP in a manner dependent on mTORC1 (21). It has also been found that the physiologic induction of SREBP1c by insulin in hepatocytes is sensitive to rapamycin (22). Like

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HIF1α, we find that mTORC1 signaling also increases the transcript levels of both *Srebp1* and *Srebp2* (2). However, SREBP1 is known to strongly induce its own transcription (23), and this is further shown in our study. Importantly, a specific increase in the levels of processed active SREBP1 is detected in cells lacking the TSC1-TSC2 complex, and this increase is sensitive to rapamycin (2). The mTORC1-stimulated increase in processed SREBP1 occurs independently of GSK3 or effects on SREBP1 protein stability. Knockdown experiments showed that S6K1 is required downstream of mTORC1 for accumulation of processed SREBP1 and expression of its target genes in this setting. A role for S6K1 in the activation of SREBP is consistent with genetic studies in *Drosophila*, in which the orthologs of both S6K1 and SREBP have been found to be critical for the ability of *Drosophila* TORC1 to promote an increase in cell and organ size (21, 24).

Although the mechanism is currently unknown, our data are consistent with S6K1 regulating a step in the complex processing of the SREBPs. A previous study has suggested that a pathway downstream of PI3K and Akt stimulates the trafficking of full-length SREBP2 to the Golgi, where it is processed and activated (25). It has also been reported that ER stress can promote SREBP trafficking and activation in an adaptive mechanism to expand the ER (26–28). However, despite elevated basal levels of ER stress in cells and tumors lacking the TSC1-TSC2 complex because of uncontrolled mTORC1 signaling (29), this mechanism does not seem to contribute to the activation of SREBP, as knockdown of S6K1 blocks SREBP1 activation without relieving ER stress in these cells (J.L. Yecies and B.D. Manning, unpublished data). We hypothesize that S6K1 plays a more direct role, phosphorylating and regulating one of the many proteins involved in ER retention, trafficking, or proteolytic processing of SREBP. However, at this stage, additional S6K-independent mechanisms regulating SREBP activation downstream of mTORC1 cannot be ruled out, and future studies will undoubtedly reveal the molecular mechanism(s).

Implications for Tumor Development, Progression, and Treatment

Increased aerobic glycolysis (the Warburg effect) and *de novo* lipogenesis are the 2 most commonly detected metabolic changes in tumors and can be considered the metabolic hallmarks of cancer. Our study to uncover the downstream consequences of mTORC1 activation, a common event in human cancer (5), shows that mTORC1 signaling is sufficient to drive these metabolic processes (2). mTORC1 promotes these metabolic changes through induction of a transcriptional program affecting metabolic gene targets of HIF1α and SREBP1 and 2. Although the glucose transporters and glycolytic enzymes encoded by HIF1α are well known to be upregulated in tumors (13), less is known about the expression status of the diverse array of SREBP targets. One notable exception is *fatty acid synthase* (*FASN*), which encodes a multifunctional enzyme complex that converts acetyl-CoA to the 16-carbon saturated fatty acid palmitate. Because most normal tissues do not undergo substantial levels of *de novo* lipid biosynthesis, obtaining lipids from dietary sources instead, FASN levels are low in most tissues. However, FASN is transcriptionally upregulated in most types of human cancer (30). Oncogenic activation of the PI3K-Akt pathway has been implicated in the increased expression of FASN in ovarian and prostate cancer (31). Our findings that mTORC1 signaling can stimulate FASN expression through SREBP suggest that mTORC1 might play a critical role in FASN expression and lipogenesis in human cancers characterized by activation of the PI3K-Akt pathway. Interestingly, we found that the SREBPs are essential for mTORC1-driven cell proliferation (2), suggesting that specific enzymes encoded by gene targets of these transcription factors could represent novel targets for cancer therapeutics. To this end, many studies have suggested efficacy of FASN inhibitors in preclinical tumor models (32). Inhibiting lipid biosynthesis may be particularly effective in settings of aberrantly high mTOR activity, which drives uncontrolled protein synthesis, as lipids are required for biogenesis of not only plasma membrane but also ER. Indeed, knockdown of SREBP1 and SREBP2 in TSC2-deficient cells further exacerbates mTOR-driven ER stress (J.L. Yecies and B.D. Manning, unpublished data).

In addition to lipogenesis, a number of other processes are induced by SREBP that could contribute to the tumor-promoting activities of mTORC1. SREBP stimulates the expression of genes involved in the synthesis of isoprenoids, which modify many signaling proteins, including members of the Ras superfamily, and could contribute to cancer pathogenesis. The observation that acetyl-CoA, derived from the reaction catalyzed by the SREBP target ATP-citrate lyase, is required for histone acetylation (33) suggests a potential role for global regulation of chromatin downstream of mTORC1. Perhaps most notable is our finding that mTORC1 increases flux through the oxidative arm of the pentose phosphate pathway and regulates expression of the rate-limiting enzyme in this pathway (G6PD) through SREBP1. Relative to glycolysis and lipogenesis, dysregulation of the pentose phosphate pathway in cancer has received much less attention in the field of tumor cell metabolism, despite mounting evidence for the importance of this pathway in tumor development and progression. A causal role for G6PD in tumorigenesis was shown by its ability to transform NIH-3T3 cells (34), and G6PD has been found to be elevated in animal tumor models (35, 36) and human neoplasms of the breast, endometrium, cervix, lung, and prostate (37–41). Through the production of NADPH, upregulation of the oxidative pentose phosphate pathway is likely to represent an important mechanism by which some tumor cells meet the unique metabolic demands of rapid anabolic growth and proliferation. In addition, G6PD-produced NADPH is important for regenerating reduced glutathione oxidized in the protection against reactive oxygen species (ROS). Tumor cells may benefit from upregulation of this pathway to control elevated ROS levels resulting from the fluctuating availability of oxygen and nutrients in the tumor microenvironment. It will be important for future studies to determine whether there are also SREBP-independent inputs into the regulation of the pentose phosphate pathway

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downstream of mTORC1 and whether mTORC1 signaling promotes resistance to oxidative stress.

Our findings show that mTORC1 activation alone is sufficient to drive specific metabolic processes that are frequently detected in human cancers. Aberrant activation of mTORC1 occurs in the most common human cancers, suggesting that mTORC1 signaling contributes to the metabolic reprogramming of cancer cells, thereby affording survival and proliferative advantages. Targeting these downstream metabolic pathways may provide effective therapeutic approaches for mTORC1-driven tumor syndromes (e.g., TSC) and sporadic cancers. Inhibitors targeting the metabolic enzymes comprising these pathways are unlikely to elicit the same unwanted feedback signaling events that have been proposed to limit the usefulness of rapamycin and its analogues in the clinic. Therefore, it is possible that such metabolic inhibitors would elicit selective cytotoxic responses in the tumor, rather than the cytostatic effects routinely seen with rapamycin (42). Finally, given the sheer number of oncogenes and tumor suppressors lying upstream of mTORC1, it will be important to identify the oncogenic settings in which mTORC1 signaling is the major driver of these common metabolic changes. It seems likely that parallel pathways downstream of oncogenes, such as PI3K and RAS, will also contribute to the control over these metabolic parameters within different tumors. It is this complexity that we must understand in order to develop therapeutic strategies aimed at tumor-specific cell metabolism.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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