Akt-Dependent Glucose Metabolism Promotes Mcl-1 Synthesis to Maintain Cell Survival and Resistance to Bcl-2 Inhibition

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Abstract

Most cancer cells utilize aerobic glycolysis, and activation of the phosphoinositide 3-kinase/Akt/mTOR pathway can promote this metabolic program to render cells glucose dependent. Although manipulation of glucose metabolism may provide a means to specifically eliminate cancer cells, mechanistic links between cell metabolism and apoptosis remain poorly understood. Here, we examined the role and metabolic regulation of the antiapoptotic Bcl-2 family protein Mcl-1 in cell death upon inhibition of Akt-induced aerobic glycolysis. In the presence of adequate glucose, activated Akt prevented the loss of Mcl-1 expression and protected cells from growth factor deprivation-induced apoptosis. Mcl-1 associated with and inhibited the proapoptotic Bcl-2 family protein Bim, contributing to cell survival. However, suppression of glucose metabolism led to induction of Bim, decreased expression of Mcl-1, and apoptosis. The proapoptotic Bcl-2/Bcl-xL/Bcl-w inhibitor, ABT-737, shows clinical promise, but Mcl-1 upregulation can promote resistance. Importantly, inhibition of glucose metabolism or mTORC1 overcame Mcl-1-mediated resistance in diffuse large B cell leukemic cells. Together these data show that Mcl-1 protein synthesis is tightly controlled by metabolism and that manipulation of glucose metabolism may provide a mechanism to suppress Mcl-1 expression and sensitize cancer cells to apoptosis. Cancer Res; 71(15): 5204–13. ©2011 AACR.

Introduction

Many cancer cells have increased rates of glucose uptake and glycolysis relative to their normal counterparts, a metabolic program termed aerobic glycolysis (1, 2) that has allowed detection and imaging of tumors and metastases by 18F-deoxyglucose positron emission tomography (3). This metabolic program is believed to promote biosynthesis for rapid cell growth and inhibit some cell death pathways (4, 5). In particular, we have shown that elevated glycolysis characteristic of cancer cells can affect Bcl-2 family proteins to suppress induction of the proapoptotic protein Puma and degradation of the antiapoptotic protein Mcl-1 (6–9). Because cancer cells often rely on glucose as a biosynthetic and energy source, disruption of aerobic glycolysis may provide an efficient means to selectively target and eliminate cancer cells.

Bcl-2 family proteins are likely critical to effectively induce apoptosis in new metabolic approaches to cancer therapy, as inhibition of glucose metabolism requires Bcl-2 family proteins to initiate rapid apoptosis. Cells lacking the proapoptotic Bcl-2 family proteins Bax and Bak resist cell death for prolonged periods of nutrient starvation through activation of autophagy and use of alternate fuels (10). In addition, the Bcl-2 family includes antiapoptotic proteins such as Bcl-2, Bcl-xL, and Mcl-1, and proapoptotic BH3-only proteins, including Puma and Bim (11), and expression of antiapoptotic family members can protect cells from apoptosis upon glucose deprivation (8, 12). In addition, we have previously shown that glucose deprivation can lead to induction of Bim and a p53-dependent increase in Puma expression that contributes to apoptosis (8, 9).

Among Bcl-2 family proteins, Mcl-1 may play a particularly important role in cell death responses to changes in glucose metabolism (7, 13, 14). Mcl-1 was first identified in a myeloid cell leukemia cell line (15) and is overexpressed in many cancers, including B- and T-cell malignancies (16). In contrast, genetic deletion of Mcl-1 can cause embryonic lethality (17), impede lymphocyte survival (18, 19), and sensitize cancer cells to treatment with other agents (20–22). Synthesis of Mcl-1 is regulated through transcriptional mechanisms induced by cytokines including interleukin (IL)-2, -3, and -7, as well as by control of protein translation through mTOR (14, 23). When translated, Mcl-1 is a short-lived protein that is subject to...
rapid degradation after phosphorylation through ubiquitin-dependent (24–27) and ubiquitin-independent pathways (28).

We have previously shown that the oncogenic kinase Akt promotes glucose metabolism and requires glucose in part to regulate Bcl-2 family proteins to prevent cell death (4, 9). Here, we examine the role of glucose metabolism in cells with active Akt and show that inhibition of glucose metabolism leads to a decrease in Mcl-1 protein expression that greatly sensitizes cells to ABT-737, a BH3 mimic that functions by binding to and inhibiting the antiapoptotic function of Bcl-2, Bcl-xL, and Bcl-w, but not Mcl-1 or A1 (29). These results suggest that cancer cell glucose metabolism is essential to maintain mTOR and 4E-BP1 phosphorylation to sustain Mcl-1 protein translation and that therapies directed at aerobic glycolysis may allow selective reduction of Mcl-1 to sensitize cancer cells to apoptosis to ABT-737.

Materials and Methods

Cell culture

Control, myristoylated Akt (mAkt), mAkt+ p70 S6K1 E389-D389 (mAkt + CA-S6K1), and Bcl-xL expressing FL5.12 cells were cultured as described (7, 12) and washed with PBS followed by culture ± IL-2. mAkt was induced by 16- to 24-hours treatment with 1 µg/ml doxycycline (Sigma). Jurkat cells (American Type Culture Collection) were cultured in RPMI 1640 media with 10% FBS. Murine primary T cells were isolated by negative selection (StemSep) and stimulated on anti-CD3e and anti-CD28-coated plates (BD Pharmingen) in RPMI 1640 media with 10% FBS and 5 ng/mL IL-2 (PeproTech). After 48 hours, T cells were washed and cultured for an additional 24 hours with IL-2. DHL4 Par, DHL4 R2, Ly.1 Par, Ly.1 R7, and Ly.1 R10 cells were provided by Dr. A. Letai (Dana Farber Cancer Institute, Boston, MA; ref.20). DHL4 cells were cultured in Iscoves Modified Dulbecco’s modified Eagle’s medium (Mediatech) with 10% FBS. Ly.1 cells were cultured in RPMI 1640 media with 10% FBS. Glucose starvation was accomplished by washing 3× with PBS and culture in glucose-free RPMI 1640 media (Gibco) with 10% dialyzed FBS (Gemini BioProducts). 2-Deoxyglucose (2DG; Sigma), cycloheximide (CHX; Sigma), PP242 (Sigma), rapamycin (Cell Signaling), and ABT-737 (Abbott Laboratories) were added at indicated doses.

Immunoblots

Immunoblots were visualized by using Supersignal West Pico Chemiluminescent Substrate (Thermo Scientific) or the Odyssey infrared imagining system (LiCor). Images were uniformly contrasted and some were digitally reorganized to ease interpretation (indicated by white spaces).

Immunoprecipitations

Cells were harvested in 1% CHAPS buffer with protease (BD Pharmingen) and phosphatase (Sigma) inhibitors. Anti–Mcl-1 antibody (BioLegend) was added to equal protein amounts and precipitated with protein A/G beads (Santa Cruz) in 1% CHAPS buffer.

Cell death analysis

Cells were stained with 1 µg/mL propidium iodide (PI; Invitrogen), and 5,000 cells were analyzed on a FACScan flow cytometer (BD Biosciences) in triplicate and analyzed with FlowJo software (TreeStar).

Quantitative real-time PCR

RNA was harvested by using TRizol solution (Invitrogen) and reverse transcribed with SuperScript II RT (Invitrogen) for quantitative real-time PCR with IQ SYBR Green Supermix (BioRad) and β2-microglobulin (8) and Mcl-1 primers (GCATGCTCCGGAACGTGACATTA and ACGTGAAGAAC-TCCACAAAAACCA).

Transfection and plasmids

Transfection transfections were conducted by nucleofection (Amaxa Kit V; Lonza). Bim, Mcl-1, and control short hairpin RNA interference (shRNAi) constructs have been described (7). FLAG-tagged mouse Bim in the pEF6 vector was used for Bim overexpression.

Mcl-1 synthesis

Control and/or mAkt expressing FL5.12 cells were cultured for 8 hours as indicated, washed, and cultured in cysteine and methionine-free RPMI 1640 media (Mediatech) for 30 minutes. 35S-labeled cysteine and methionine (Perkin Elmer) were added, cells were harvested at the indicated times. Mcl-1 was immunoprecipitated, and synthesis rate was determined by using the following formula: t1/2 = LN(2)/slope of 35S incorporation.

Metabolic measurements

ATP levels were determined by using the ATP bioluminescence assay Kit CLS II (Roche Applied Science). Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured in real-time by using an XF24 extracellular flux analyzer (Seahorse Bioscience) as previously described (30).

Statistical analyses

Statistical significance was determined by Student’s t-test with P values as indicated with an asterisk.

Results

Active Akt must maintain Mcl-1 in a glucose-dependent fashion to suppress Bim-induced cell death after IL-3 deprivation

Constitutive Akt activation occurs in many cancers to promote aerobic glycolysis and glucose-dependent cell
survival (4, 12). Because Mcl-1 and Bim are known to play prominent roles in hematopoietic cell survival (18, 19, 31), we hypothesized that these proteins may be subject to metabolic regulation in Akt-mediated cell survival. Expression of either mAkt or Bcl-xL prevented cell death after IL-3 withdrawal of FL5.12 cells, but only mAkt required glucose for survival (Fig. 1A; refs. 9, 12). To assess possible regulation of Bcl-2 family members by Akt-dependent glucose metabolism and to avoid changes in Mcl-1 and Bim as a consequence of apoptosis itself (32), we examined Mcl-1 and Bim in cells expressing Bcl-xL or mAkt. In Bcl-xL expressing cells, growth factor or glucose deprivation each led to decreased Mcl-1 expression and induction of Bim, particularly in the absence of IL-3 (Fig. 1B). In mAkt expressing cells, Bim was induced upon limitation of either growth factor or glucose. In contrast, although activated Akt maintained Mcl-1 expression upon IL-3 withdrawal, Mcl-1 levels decreased when glucose was withdrawn. This was not because of decreased Akt signaling, as both Akt and the Akt substrate GSK-3 remained phosphorylated in the absence of glucose (Supplementary Fig. S1A). Decreased Mcl-1 expression upon disruption of glucose metabolism appeared specific among antiapoptotic Bcl-2 family proteins, as glucose deprivation did not affect expression of Bcl-2 or Bcl-xL (Supplementary Fig. S1B).

Importantly, the glucose-dependent ability of mAkt to maintain Mcl-1 expression was essential for maximal Akt-mediated survival. Partial reduction of Mcl-1 expression by shRNAi was sufficient to reduce survival of mAkt expressing cells relative to Bcl-xL expressing cells that resist apoptosis and to more closely resemble control FL5.12 cells that undergo rapid cell death after IL-3 withdrawal (Fig. 1C and D, and Supplementary Fig. S2A and B). Dependence on Mcl-1 was not because of a specific unique function of Mcl-1, as overexpression of Bcl-2 family proteins, as glucose deprivation did not affect expression of Bcl-2 or Bcl-xL (Supplementary Fig. S1B).

Inhibition of glucose metabolism causes decreased Mcl-1 expression and cell death in multiple settings

Because glucose can be exhausted in inflamed tissues or tumors (33), glucose availability may act as a rheostat to control Mcl-1 expression and cell death. To examine the metabolic effects of glucose depletion, control, mAkt, and Bcl-xL expressing cells were cultured in the presence or absence of glucose for 12 hours, and ATP and metabolic flux were analyzed. Despite the availability of alternative fuel sources, glucose deprivation decreased ATP levels in control, mAkt, and Bcl-xL expressing cells (Fig. 2A). Bim deficiency partially rescued the increased apoptosis observed in IL-3-deprived mAkt expressing cells with reduced Mcl-1 (Fig. 2B). Conversely, transfection of control cells with Bim led to rapid toxicity (Fig. 2C and D). mAkt and Bcl-xL could each partially suppress Bim-induced apoptosis, but mAkt expressing cells failed to do so when Mcl-1 levels were reduced by shRNAi. These data suggested a functional relationship between Mcl-1 and Bim, and immunoprecipitation with an anti-Mcl-1 antibody revealed increased Bim binding to Mcl-1 after IL-3 withdrawal (Fig. 2E). Therefore, Mcl-1 expression is required to suppress apoptosis induced by Bim and other Bcl-2 family members (5, 8) upon disruption of glycolysis.

Figure 1. Glucose-dependent maintenance of Mcl-1 is essential for Akt-mediated cell survival. A, control, Bcl-xL, and mAkt expressing FL5.12 cells were cultured as indicated and assayed for cell death by PI exclusion after 24 hours. B, Bcl-xL and mAkt expressing cells were transfected with control and Mcl-1 shRNAi and examined (C) by immunoblot and (D) cultured –IL-3 and assayed for cell death by PI exclusion after 24 hours. Representative experiments are shown and values represent the means ± standard deviations of triplicate samples.
ECAR, a measurement indicative of glycolytic rate (Fig. 3B). Surprisingly, in no case did cells increase their OCR after 12 hours of glucose deprivation (Fig. 3C). Thus, glucose deprivation for extended periods led to decreased ATP and mitochondrial oxidative metabolism did not increase to compensate.

To more closely examine glucose metabolism and Mcl-1, control FL5.12 cells were cultured either in limiting doses of glucose or in the presence of glucose and the glycolytic inhibitor 2DG. Complete glucose deprivation caused decreased Mcl-1 expression (Fig. 4A) and rapid cell death (Fig. 4B). As little as 0.1 mmol/L glucose protected Mcl-1 and prevented cell death by PI exclusion. Mcl-1 was immunoprecipitated (IP) from control and mAkt expressing cells cultured IL-3 for 10 hours and analyzed by immunoblot. Representative experiments are shown, and values represent the means ± SD of triplicate samples. Statistical significance is indicated with *, P < 0.05.

Glucose metabolism is essential to maintain Mcl-1 protein synthesis
Mcl-1 is frequently regulated at the level of protein stability (7, 24-26). To determine if Akt maintained Mcl-1 levels by glucose-dependent suppression of proteolytic degradation, mAkt expressing FL5.12 cells were cultured in the absence of IL-3 and the presence and absence of glucose followed by treatment with CHX to inhibit new protein synthesis (Fig. 5A). Surprisingly, glucose deprivation did not significantly decrease Mcl-1 protein half-life. Mcl-1 mRNA can also be unstable (34) and Mcl-1 transcription is highly regulated, but real-time PCR also did not reveal additional significant changes in Mcl-1 mRNA levels upon glucose deprivation beyond what occurred upon IL-3 withdrawal (Fig. 5B).

Akt can promote protein synthesis through the activation of mTORC1, and interruption of this pathway may decrease both the T-ALL cell line Jurkat (Fig. 4F) as well as stimulated primary murine T cells (Fig. 4G) also caused decreased Mcl-1 expression.

Figure 2. Mcl-1 inhibits Bim-induced apoptosis. A and B, mAkt expressing cells were transfected with control, Mcl-1, and/or Bim shRNAi, cultured IL-3, and analyzed by (A) immunoblot after 10 hours or (B) for cell survival after 24 hours IL-3. C and D, control, mAkt, and Bcl-xL expressing cells were transfected with control or Bim expression plasmids Mcl-1 shRNAi and cells were examined by (C) immunoblot and (D) assayed for cell death by PI exclusion. E, Mcl-1 was immunoprecipitated (IP) from control and mAkt expressing cells cultured IL-3 for 10 hours and analyzed by immunoblot. Representative experiments are shown, and values represent the means ± SD of triplicate samples. Statistical significance is indicated with *, P < 0.05.
Mcl-1 after glucose deprivation. Indeed, metabolic stress has been reported to promote AMP-activated protein kinase activation to inhibit mTORC1 and lead to decreased Mcl-1 synthesis (14). Mcl-1 synthesis rates were, therefore, directly measured in control and mAkt expressing FL5.12 cells by 35S metabolic labeling and Mcl-1 immunoprecipitation. IL-3 deprivation led to a decrease in Mcl-1 synthesis in control cells that was inhibited by mAkt expression (Fig. 5C). Importantly, the ability of mAkt to prevent the decrease in Mcl-1 synthesis upon IL-3 deprivation was dependent on glucose metabolism, as glucose deprivation of mAkt cells sharply decreased Mcl-1 synthesis (Fig. 5D).

**Control of Mcl-1 synthesis by the mTORC1/4EBP1 pathway**

Akt promotes protein synthesis by stimulating mTORC1 to phosphorylate S6 kinases (S6K) and 4EBP1 (35). Recent data have shown that these 2 pathways of mTORC1 function can be...
differentially regulated and functionally distinct, with inhibitory phosphorylation of 4EBP1 important to promote protein synthesis while stimulatory phosphorylation of the S6K pathway promotes cell growth and metabolism (36). IL-3 deprivation of control cells reduced mTORC1 activity and decreased phosphorylation of 4EBP1 as well as S6K and the S6K substrate, S6 (Fig. 6A; quantitative analyses of phosphorylation provided under each blot). Importantly, total S6 levels were unaffected by the presence or absence of IL-3 and/or glucose (Supplementary Fig. S3). Although IL-3 deprivation of mAkt expressing cells led to a sharp decrease in phospho-S6, constitutively active Akt partially sustained phospho-4EBP1 in the presence of glucose. Glucose deprivation of IL-3 deprived mAkt expressing cells, however, led to further decreased phosphorylation of components of both mTORC1 effector pathways, with reduced phospho-S6 and phospho-4EBP1. These data suggested that mAkt maintained Mcl-1 translation partially via the mTOR/4EBP1 pathway rather than through S6K/S6. To directly test the role of S6K in regulation of Mcl-1 levels, cells expressing mAkt alone or together with a constitutively active form of S6K (p70 S6K1 E389-D3E) were cultured in the presence or absence of IL-3 or glucose (Fig. 6B). Although S6 remained phosphorylated, glucose deprivation nevertheless led to decreased Mcl-1 levels, showing that the S6K1/S6 pathway is not sufficient to support Mcl-1 expression.

Because Akt relied on glucose to maintain Mcl-1 protein synthesis via inhibition of 4EBP1, direct inhibition of mTORC1 may provide a means to limit protein translation and thus suppress Mcl-1 expression because of its short half-life. The mTORC1 inhibitor rapamycin has shown mixed results in cancer clinical trials (37), and recent studies have showed that it does not completely block 4EBP1 phosphorylation (38). Therefore, we treated cells with an active site kinase inhibitor of mTOR, PP242, that efficiently inhibits both S6 and 4EBP1 phosphorylation (39). In both control and mAkt expressing FL5.12 cells, PP242 treatment readily inhibited both S6 and 4EBP1 phosphorylation and led to decreased levels of Mcl-1 (Fig. 6C). mTOR kinase inhibition also impeded mAkt-mediated cell survival (Fig. 6D).

Inhibition of glycolysis overcomes ABT-737 resistance in diffuse large B cell lymphoma cells

The Bcl-2, Bcl-xL, and Bcl-w inhibitor ABT-737 has shown promise to promote apoptosis of cancer cells, but overexpression of Mcl-1 leads to resistance (20, 21, 40). Therefore, inhibition of glycolysis or mTOR kinase activity, to reduce Mcl-1 protein levels, may restore sensitivity to ABT-737-resistant cancer cells performing aerobic glycolysis. To test this hypothesis, ABT-737-resistant variants of the diffuse large B cell lymphoma (DLBL) cell lines Ly.1 and DHL4 (20) were examined for synergistic induction of apoptosis by combined glycolysis inhibitors and ABT-737.
glycolysis inhibition and ABT-737. By using increasing doses of ABT-737, each cell line was shown more resistant to ABT-737 treatment than the parental strains (Supplementary Fig. S4A and B; ref. 20). Resistance to ABT-737 appeared because of elevated Mcl-1 in Ly.1 R7 and Ly.1 R10 and elevated Mcl-1 together with increased A1 in DHL4 R2 (ref. 20; Supplementary Fig. S4C). Consistent with similar antiapoptotic roles for Mcl-1 and Bcl-2 or Bcl-xL, neither 2DG treatment to inhibit glycolysis nor ABT-737 treatment alone were sufficient to cause death of the resistant cell lines (Fig. 7A). Combined treatment with 2DG and mAkt expressing cells were cultured as indicated for 10 hours and analyzed by immunoblot with quantitation. B, cells expressing mAkt constitutively active S6K1 (CA-S6K1; p70 S6K1 E389-D3E) were cultured as indicated for 10 hours and analyzed by immunoblot. C and D, control and mAkt expressing cells were cultured as indicated with or without the mTOR kinase inhibitor PP242 (1 μmol/L) and analyzed (C) by immunoblot after 10 hours or (D) for cell viability by PI exclusion. Representative experiments are shown and values represent the means ± SD of triplicate samples.

Discussion

The highly glycolytic metabolic phenotype of cancer cells was first observed by Otto Warburg nearly a century ago (2). Molecular links between aerobic glycolysis and apoptosis that may provide a selective approach to target cancer cells for apoptosis, however, are poorly understood. Here, we show that inhibition of glucose metabolism can promote or sensitize cancer cells to apoptotic cell death by decreased mTORC1/4EBP1-dependent Mcl-1 translation that allows toxicity of proapoptotic Bcl-2 family proteins, including Bim. Importantly, metabolic or mTOR kinase inhibition reduced Mcl-1 protein levels and overcame resistance to the Bcl-2 inhibitor ABT-737, suggesting this pathway may provide a mechanism to exploit aerobic glycolysis and promote cancer cell apoptosis either alone or as combinatorial therapy.

Aerobic glycolysis is induced in many cancers as a consequence of oncogenic kinase activity such as through the phosphoinositide 3-kinase/Akt/mTOR pathway (4, 12, 41). Importantly, Akt can also suppress alternative metabolic pathways, such as suppression of lipid uptake and oxidation through phosphorylation of carnitine palmitoyltransferase 1 (42) or by inhibition of autophagy as an alternate nutrient...
source in metabolically stressed cells (43). The overall effect, therefore, is to render cells with constitutively active Akt dependent on glucose availability and glycolytic metabolism whereas normal cells can retain greater metabolic flexibility. Thus, although all cells utilize glucose as fuel, cancer cells may be particularly sensitive to glycolytic inhibition to reduce Mcl-1. Coupling inhibition of glucose metabolism with targeted treatments may further selectively impact cancer cells (6).

This study has further implicated the importance of the mTORC1/4EBP1 pathway in metabolic stress to regulate Mcl-1 protein synthesis. Mcl-1 is highly regulated and distinguished from Bcl-2 and Bcl-xL by a short half-life and enhanced reliance on continued translation. Decreased rates of Mcl-1 synthesis in response to metabolic stress, coupled with its rapid turnover, reduced Mcl-1 expression to sensitize cells to apoptosis. Importantly, changes in Mcl-1 expression observed here were modest yet sufficient to allow Bim-mediated toxicity, highlighting the importance of this pathway. Also, it is likely that inhibition of glucose metabolism or mTOR kinase activity does not specifically reduce Mcl-1 translation, but inhibits general protein synthesis (36). However, because of the very short half-life of Mcl-1 relative to other antiapoptotic Bcl-2 family members, Mcl-1 levels may be a central determinant in cell death when glucose metabolism is disrupted.

The mechanism by which inhibition of glucose metabolism inhibits mTORC1-dependent phosphorylation of 4EBP1 and Mcl-1 translation remains unclear. Our data show that inhibition of glycolysis causes decreased ATP levels, for which oxidative metabolism cannot fully compensate. This may lead to activation of AMPK, resulting in the inhibition of mTORC1 activity and suppression of Mcl-1 translation (14, 44–47). Inactivation of all mTOR activity, however, would decrease Akt phosphorylation, as mTORC2 is the Akt serine 473 kinase (48). 2DG treatment or glucose deprivation of cells with oncogenic Akt, however, did not reduce Akt S473 phosphorylation or phosphorylation of the Akt substrate, GSK3. In contrast, the mTOR inhibitors rapamycin and PP242 each decreased phospo-Akt, suggesting that glucose deprivation causes specific inhibition of mTORC1 in a manner distinct from either rapamycin or PP242. A more detailed understanding of how glucose deprivation can affect mTOR activity
in the context of cancer cells to selectively block mTORC1 will be essential in understanding how metabolism-targeted therapies might enhance cell death.

We have previously shown that glucose deprivation leads to induction of the proapoptotic Bcl-2 family proteins Puma and Bim, and reduced levels of Mcl-1 (8, 9). Similarly, glucose deprivation of activated T cells and other cancer cells can lead to reduced levels of Mcl-1 (13, 14). Regulation of the balance of Bcl-2 family proteins by glucose metabolism may be a critical aspect of how aerobic glycolysis can affect cell fate. Many cancer cells are considered primed for apoptosis by upregulation of proapoptotic BH3 only proteins, such as Bim, Puma, or Noxa, to occupy antiapoptotic Bcl-2, Bcl-xL, and Mcl-1 (49). Metabolic status and nutrient availability may alter the primed state of cancer cells to influence susceptibility to other cancer therapeutics that induce apoptosis. It is the unique dependence of Mcl-1 on cell metabolism that places it as a central regulator of cell survival to inhibit proapoptotic proteins, including Bim, upon disruption of cancer metabolism.

Metabolically-targeted therapies offer promising pharmacologic targets for cancer therapy. Antia apoptotic Bcl-2 family proteins Bcl-2, Bcl-xL, and Mcl-1, however, must be overcome to promote cancer cell death. Mcl-1 levels have been closely associated with resistance to the Bcl-2/Bcl-xL inhibitor ABT-737 (20-22, 40, 50), and our data show that inhibition of aerobic glycolysis or mTOR kinase activity can suppress protein synthesis leading to a reduction in Mcl-1 levels that sensitizes cells to cytotoxicity mediated by Bim and potentially other proapoptotic Bcl-2 family proteins (36). Metabolic control of Mcl-1 synthesis, therefore, is essential for growth factor independent survival of cancer cells, and metabolism-targeted therapies may provide useful options for novel cancer treatments to reduce Mcl-1 and increase cancer cell apoptotic sensitivity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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