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Review

Cell metabolism: An essential link between cell growth and apoptosis ☆

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ABSTRACT

Growth factor-stimulated or cancerous cells require sufficient nutrients to meet the metabolic demands of cell growth and division. If nutrients are insufficient, metabolic checkpoints are triggered that lead to cell cycle arrest and the activation of the intrinsic apoptotic cascade through a process dependent on the Bcl-2 family of proteins. Given the connections between metabolism and apoptosis, the notion of targeting metabolism to induce cell death in cancer cells has recently garnered much attention. However, the signaling pathways by which metabolic stresses induce apoptosis have not as of yet been fully elucidated. Thus, the best approach to this promising therapeutic avenue remains unclear. This review will discuss the intricate links between metabolism, growth, and intrinsic apoptosis and will consider ways in which manipulation of metabolism might be exploited to promote apoptotic cell death in cancer cells. This article is part of a Special Issue entitled Mitochondria: the deadly organelle.

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1. Introduction

Throughout the lifespan of an individual, the body must continually balance cell growth and proliferation with cell death to support proper development and maintain healthy homeostasis of mature tissues. A central mechanism to control this balance is the dependence of each cell on survival cues from its microenvironment [1]. Indeed, the processes of embryogenesis, developmental patterning, and maintenance of adult tissue require that cells receive proper growth signals. This social control model ensures that cells that receive the appropriate cues can survive and proliferate, while cells that fail to receive sufficient access to these signals, such as excess or damaged cells, undergo apoptosis, or programmed cell death. These perpetual processes of cell growth, proliferation, and death are essential for the optimal function of nearly all tissues and organ systems within the body, and must be properly coordinated. If cell proliferation lags or cell death is in excess, degenerative diseases may result; if proliferation exceeds death, neoplastic diseases and cancer may occur. Interestingly, it has become clear over the past decade that a key mechanism by which growth signals control cell growth and death is through regulation of cell metabolism.

In addition to the basal energy needs of resting cells to maintain osmotic balance and replacement biosynthesis, strong mitogenic or growth factor stimulation leads to greatly increased metabolic demands. Specifically, the doubling of cellular contents requires that

nucleic acid, lipid, and protein synthesis be dramatically increased. To account for this increased energetic and biosynthetic demand, growth factors upregulate metabolic pathways essential for proliferation [2] and, in particular, dramatically increase rates of glucose uptake and glycolysis. In contrast, when growth factors become limiting, for instance at the end of an immune response or if excess cells lose access to appropriate growth factors, cell metabolism, and particularly glycolysis, decreases. While cells can alter their metabolism to rely more on mitochondrial oxidation, cells will ultimately undergo apoptosis in the absence of growth factor signaling. This acute loss of glucose metabolism is a central element in the initiation of apoptosis, because maintenance of glucose uptake after withdrawal of growth factors or serum can suppress cell death [3–9]. Thus, cells rely on growth factors to maintain survival and drive proliferation, in part, because growth factors regulate cell metabolism to overcome metabolic checkpoints for proliferation and apoptosis (Fig. 1) [10].

This metabolic check on cell growth and death is most notably overridden in cancer, where oncogenic kinases can mimic growth signals, allowing cells self-sufficiency to maintain the high rates of glucose metabolism required to support cell proliferation. Specifically, cancerous cells often rely on the particular metabolic program of aerobic glycoylsis, first noted nearly a century ago by Otto Warburg [11]. With this metabolic program, cancerous cells demonstrate markedly increased rates of glucose uptake, glycolysis, and lactate production, even in the presence of normal oxygen levels, a phenomenon known as 'the Warburg effect'. It is now clear that, in most cases, both hypoxia and the very oncogenes that drive cancer cell proliferation can induce these metabolic changes.

This metabolic phenotype has drawn a great deal of attention in recent years as a potential new target in cancer therapy. Given
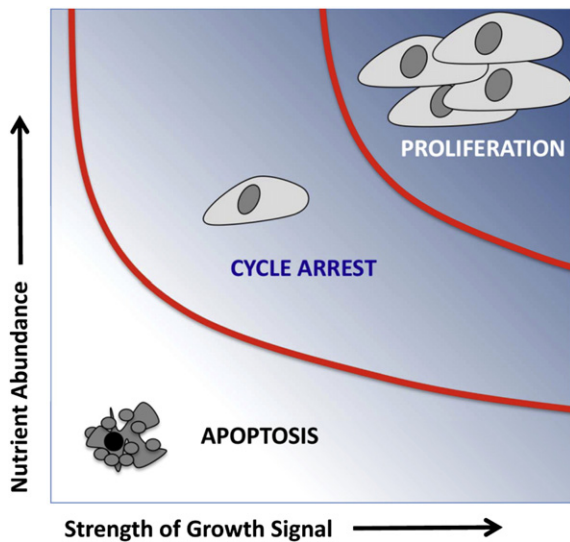
Fig. 1. Growth factor signals and nutrient availability determine cell fate. As growth factor signals increase the drive for cell proliferation and metabolic demands increase. Availability of nutrients determines if sufficient resources are present to support cell survival and growth. If insufficient nutrients are available, cells undergo apoptosis. These metabolic checkpoints to link nutrients to cell cycle arrest and apoptosis are critical elements to maintain tissue homeostasis and prevent disease.
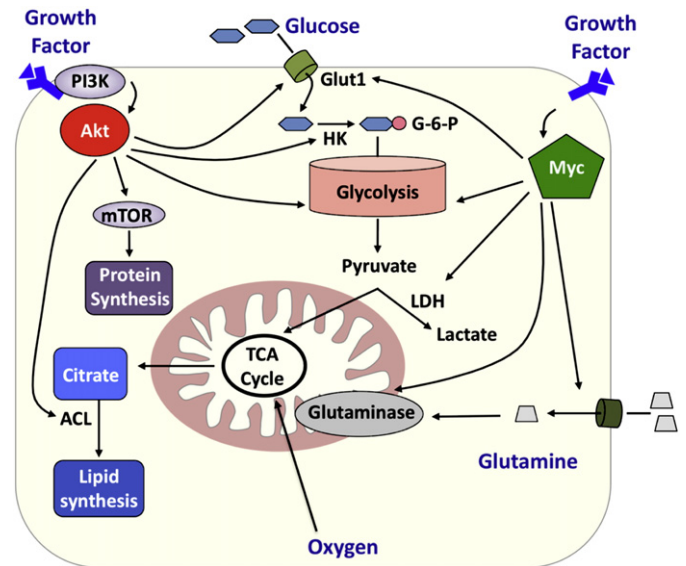

Fig. 2. Growth factor or oncogene-stimulated cell metabolism. Through regulation of signaling pathways such as Akt and Myc growth factors promote glucose and glutamine uptake for glycolysis and glutaminolysis. Inhibition with these metabolic pathways can lead to cell death but precise links between specific metabolic pathways and Bcl-2 family proteins are poorly understood.

metabolic checkpoints on cell proliferation and cell death, such an approach could be very fruitful both in cancer as well as in other instances of inappropriate cell proliferation. Ideally, a metabolic approach would exploit the dependence of cancer cells on aerobic glycolysis and metabolic checkpoints to promote cell senescence or cell death through apoptosis, autophagic cell death or necrosis. The pathways connecting cell metabolism and apoptosis, in particular, which form the molecular basis for metabolic checkpoints and would provide the most direct molecular targets for such an approach, have only recently begun to emerge. This review will focus on the interplay between cell metabolism, growth, and the mitochondrial apoptotic pathway and will discuss how changes in metabolism, such as those often seen in tumors, might be exploited to induce apoptosis.

2. Metabolic dependencies of proliferating cells

Mitogenic growth factor stimuli can dramatically increase glucose uptake and aerobic glycolysis to support the metabolic and biosynthetic demands of cell proliferation. This metabolic phenotype is shared by many highly proliferative cells and appears to be a general mechanism to allow rapid cell growth. Elevated aerobic glycolysis generates sufficient amounts of ATP to allow TCA cycle intermediates, derived from both glucose and glutamine, to exit the mitochondria and provide carbon backbones for lipid synthesis [2]. Thus, aerobic glycolysis allows proliferating cells to satisfy their unique biosynthetic requirements. However, if cell metabolism is not sufficient to meet these specific metabolic dependencies, cells arrest and do not divide and can ultimately undergo apoptosis if nutrients remain limiting.

Several key signaling pathways link proliferation and metabolism and promote dependence on glucose and glutamine as primary fuel sources in dividing cells (Fig. 2). Central among them are the phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR and Myc pathways. These pathways, which lie downstream of growth factor receptors and are commonly activated in the context of cancer, stimulate cells to utilize aerobic glycolysis [12]. In promoting glucose metabolism, Myc signaling enhances the expression of glucose transporters, as well as other glycolytic genes [13,14]. In contrast, Akt generally acts post-transcriptionally to promote the cell surface localization of glucose transporters [15–17] and enhance hexokinase [18–21] and phospho-fructokinase [22] activity.

Both of these pathways lead to increased glucose metabolism and enforce a metabolic program with specific nutrient dependencies. In addition to aerobic glycolysis, the PI3K/Akt signaling pathway promotes increased lipid synthesis and suppresses the use of lipids as fuel, leading to both increased cell growth as well as a dependency on glucose as a primary nutrient. Akt can stimulate the expression of lipogenic genes [23] and activity of ATP citrate lyase (ACL), which is required for the conversion of glucose to lipids [24], and inhibit the metabolism of other fuels, suppressing autophagy [25] as well as mitochondrial b-oxidation through decreased expression of carnitine palmitoyltransferase 1A (CPT1A) [26]. In a parallel set of pathways, Myc signaling also activates and increases dependency on glutamine metabolism [27], promoting the expression of glutamine transporters [28,29] and regulating expression of mitochondrial glutaminase at the post-transcriptional level [27].

Together, these findings demonstrate that a key function of the PI3K/Akt and Myc pathways is to prevent cells from experiencing nutrient limitation, which can override growth signals and lead to cell cycle arrest or apoptosis. If nutrients do become limiting, however, metabolically-sensitive checkpoints are activated to prevent cells from outstripping their resources. For example, the nutrient-sensitive kinase AMP-activated protein kinase (AMPK) mediates multiple metabolic checkpoints, activating p53 to induce cell cycle arrest upon glucose limitation [30] or apoptosis upon glucose withdrawal [31]. Similarly, the transcription factor carbohydrate responsive element binding protein (ChREBP) appears to be required for the redirection of glucose into lipid and nucleotide synthesis during mitogen-stimulated cell proliferation, and loss of ChREBP induces a p53-dependent cell cycle arrest [32] (Table 1). Furthermore, the loss of glucose metabolism can promote activation of the Bcl-2 family protein Bax to induce apoptosis, even when excess cytokines are available [3,33–35]. Despite these observations, however, metabolic checkpoints and metabolic stress response pathways have, on the whole, been poorly understood.

3. Mitochondria, the Bcl-2 family, and intrinsic apoptosis

Cell metabolism is tightly linked to the regulation of cell death through the mitochondria, which serve as a shared platform for metabolism and apoptosis. Cells that fail to receive sufficient nutrients first reduce metabolism and undergo cell cycle arrest. If cell

Table 1
Metabolic stress and regulation of p53.

Metabolic stress	Effect on p53	Downstream signaling/effects
Growth factor withdrawal	p53 activation without protein stabilization	Puma induction, apoptosis
Glucose deficiency	AMPK-dependent S15 phosphorylation and p53 stabilization	p21 induction, cell cycle arrest
Glucose deficiency	AMPK-dependent S46 phosphorylation and p53 stabilization	Puma induction, apoptosis
Decreased ChREBP and loss of glucose-dependent lipid and nucleotide synthesis	S15 phosphorylation without p53 stabilization	p21, MDM2, and TIGAR induction, cell cycle arrest

metabolism continues to be inadequate for cellular demands, the induction of intrinsic, or mitochondrial, apoptosis will occur. The intrinsic apoptotic pathway is closely tied to the mitochondria, as seminal work by Wang and colleagues showed that activation of this pathway was dependent on the mitochondrial protein cytochrome *c* [36]. Disruption of the outer mitochondrial membrane during apoptosis leads to release of cytochrome *c* from the mitochondrial intermembrane space into the cytosol, where it can associate with caspase 9 and Apaf1 to form the apoptosome complex [36,37]. The exact mechanisms underlying mitochondrial outer membrane permeabilization (MOMP) to allow cytochrome *c* release remain uncertain (see [38] for an extensive review of MOMP). However, it is clear that this process requires and is regulated by members of the Bcl-2 family of proteins.

The Bcl-2 family is divided into three groups, the anti-apoptotic, multi-domain pro-apoptotic, and BH3-only subfamilies [39]. The function of Bcl-2 family proteins is regulated largely by protein interactions between members of the various subgroups. Members of the anti-apoptotic group, including Bcl-2, Bcl-xL and Mcl-1, directly bind to and inhibit the action of multi-domain pro-apoptotic proteins. The multi-domain pro-apoptotic proteins consist of Bax, Bak and Bok, and the presence of Bax or Bak at the mitochondrial membrane is required for MOMP and the induction of mitochondrial apoptosis [40]. Upon activation, Bax and Bak change conformation, homo-oligomerize to form proteo-lipid pores in the mitochondrial outer membrane and initiate MOMP and cytochrome *c* release [41].

The activation of Bax/Bak and induction of MOMP is regulated by the combined effects of the anti-apoptotic BH3-only proteins. In unstressed cells, BH3-only proteins are not expressed, or are sequestered or in zymogen form, while anti-apoptotic Bcl-2 proteins bind and inhibit Bax and Bak. When cells experience stress, such as after DNA damage, growth factor withdrawal, or nutrient deprivation, BH3-only proteins respond by binding and inhibiting anti-apoptotic proteins to allow the release Bax and Bak, or by directly binding and activating Bax and Bak [42]. The mechanism by which BH3-only proteins induce Bax/Bak oligomerization and MOMP remains controversial (see [41–44] for reviews of this topic). However, it is clear that a cell's fate depends on the recognition of stress by BH3-only proteins and the resulting changes in the overall balance of pro- and anti-apoptotic Bcl-2 family members. Therefore, alterations in the levels of Bcl-2 proteins caused by various cellular processes are critical to the induction of apoptosis. Interestingly, growing evidence demonstrates that changes in cellular metabolism regulate checkpoints that control both pro- and anti-apoptotic Bcl-2 proteins to impact mitochondrial apoptosis and cell fate.

4. Metabolic stress and the Bcl-2 family

As a central component in cell metabolism and cell death pathways, mitochondria integrate growth stimuli and nutrient availability with cell death so that only cells with adequate access to

nutrients can survive. In this setting, Bcl-2 family proteins represent the crucial link between changes in cell metabolism and the control of apoptosis. Bcl-2 family proteins are regulated by a variety of metabolic stresses to promote activation of Bax and Bak and cause cell death (Fig. 3). Inadequate access to growth factor signals or inhibition of oncogenic kinases leads to decreased glucose uptake and apoptosis [3,45]. Alternatively, nutrient deficiency, such as the glucose or oxygen starvation that can occur during ischemia or when the blood supply is limited within developing tissues or tumors, also promotes activation of pro-apoptotic Bcl-2 family proteins [5,46].

4.1. Disruption of growth signals or oncogenic signaling pathways

Growth factor signaling pathways activate the PI3K/Akt pathway to promote both cell proliferation and cell metabolism. This coordinated control of growth and metabolism allows proliferating cells to meet energetic and biosynthetic demands. In cancer, activation of oncogenic kinases, loss of the tumor suppressor PTEN, or activating mutations in PI3K can all activate the PI3K/Akt pathway to promote glucose metabolism [47–49]. When these signals are lost or inhibited and Akt is inactivated, cells internalize nutrient transporters, and glucose metabolism can decrease dramatically [3,45]. While autophagy can be activated to provide a source in intracellular nutrients to cushion this sudden metabolic crisis, the acute loss of glucose metabolism nevertheless can induce metabolic stress and trigger checkpoints to initiate apoptosis [5,10].

In addition to normal growth factor signals, oncoproteins can initiate pathways that mimic growth factor signaling. Therefore, similar to cell death after deprivation of endogenous growth factors, molecularly targeted therapies that inhibit oncogenic kinases may act in part through suppression of growth signals that regulate metabolism. Indeed, the oncogenic kinase BCR-Abl, which results from the Philadelphia chromosome translocation and is often expressed in chronic myelogenous leukemia (CML), has been shown to regulate Glut1 cell surface trafficking through activation of the PI3K/Akt signaling pathway [47]. Inhibition of BCR-Abl with the molecularly targeted therapy imatinib mesylate led to acutely decreased glucose uptake and cell death [45,50]. It remains uncertain how this metabolic stress may contribute to imatinib-induced apoptosis, but given parallels between oncogenic kinase and growth factor signaling, regulation of cell metabolism may play a critical role in the action of this and potentially other kinase inhibitors.

In support of this model, BCR-Abl expression has recently been linked to metabolism through regulation of hypoxia-inducible factor 1-α (HIF-1α), which was found to be upregulated in cancers that display imatinib resistance caused by BCR-Abl overexpression [51]. In these cancers, HIF-1a expression drove glucose-dependent ribose synthesis through activation of transketolase, and treatment with oxythiamine, which inhibits transketolase, was found to overcome imatinib resistance and induce cell death. Ultimately, cell death after imatinib-treatment is dependent on pro-apoptotic Bcl-2 family members, and both Bim and Bad are thought to be important in this process [52]. Thus, metabolic links between oncogenic kinases and Bcl-2 family proteins hold tremendous clinical relevance.

To define the precise contribution of reduced glucose metabolism to cell death after growth factor withdrawal or targeted kinase inhibition, it is necessary to isolate glucose metabolism from other cell signaling events that occur downstream of growth factor receptors or oncogenic kinases. One way that this has been accomplished is by direct expression of metabolic genes to drive growth factor-independent cell metabolism. In one system, glucose-6-phosphate dehydrogenase has been overexpressed to drive glucose flux through the pentose phosphate pathway [53]. This was sufficient to enhance cellular transformation and tumorigenesis in mice, although precise mechanisms were not well defined.
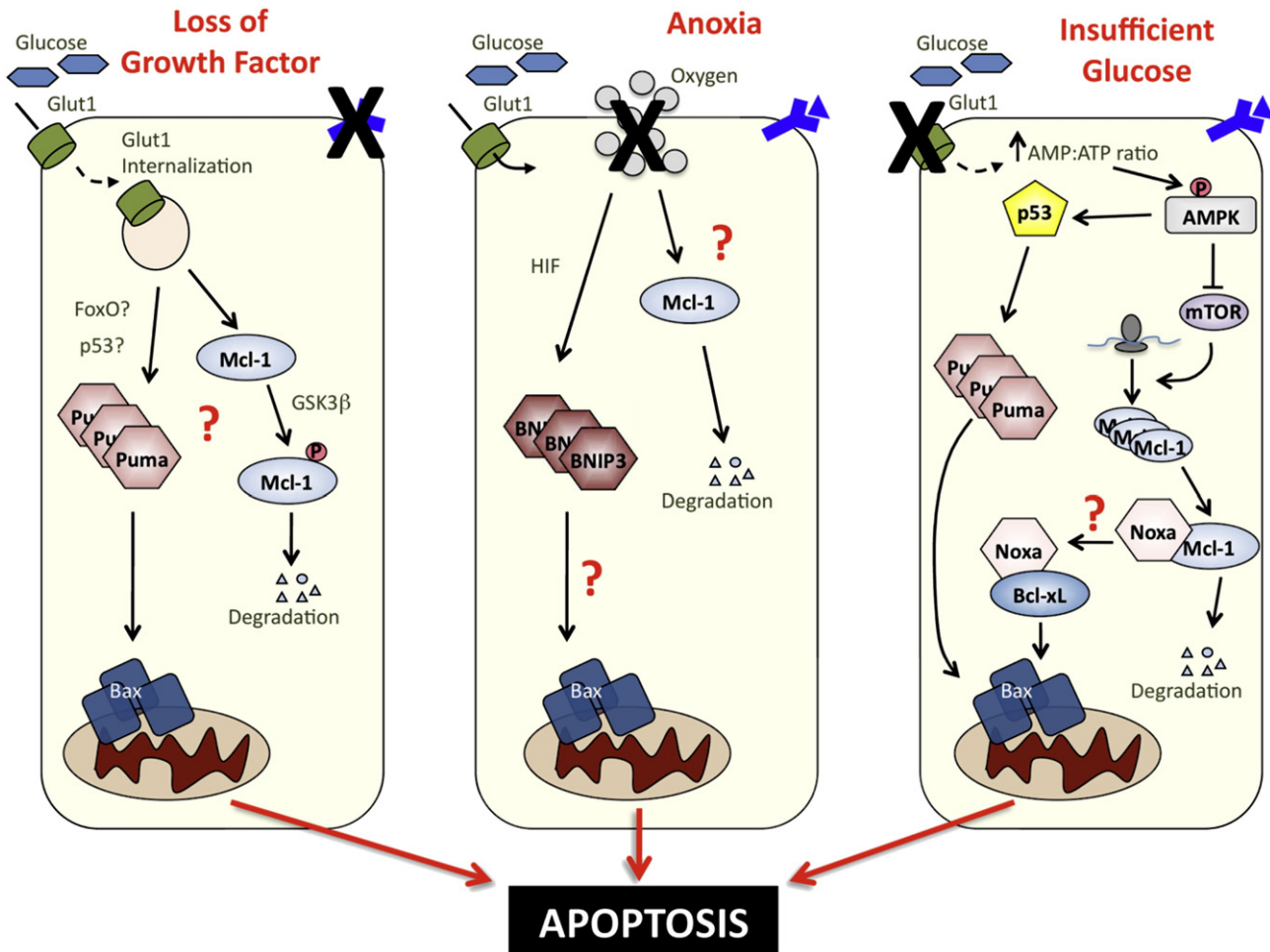
Fig. 3. Model of how metabolic stress may regulate Bcl-2 family proteins to promote apoptosis. Growth factor deprivation reduces nutrient uptake and anoxia or glucose insufficiency cause direct metabolic stress. In each case, the anti-apoptotic protein Mcl-1 and pro-apoptotic BH3-only proteins are key mediators of metabolic checkpoints to initiate Bax-mediated cytochrome *c* release and apoptosis. Specific details of regulations are uncertain and indicated by '?'.

In another approach, expression of the glucose transporter Glut1 alone or in combination with hexokinase 1 (HK1) allows cells to maintain glucose uptake to sustain both glycolysis and the pentose phosphate pathway even after growth factor withdrawal [3,4]. Consistent with a key role for the acute reduction in glucose uptake contributing to the death of growth factor-deprived cells, Glut1 and HK1 expression protected cells from Bax activation and cell death. Bax, however, was not found to be directly responsive to reduced glucose metabolism itself. Rather, Bim and Puma were essential for Bax activation upon growth factor withdrawal. These data demonstrate that upstream Bcl-2 family proteins can respond to changes in glucose metabolism in ways that ultimately result in activation of Bax.

Converse experiments, in which nutrients are withdrawn, rather than artificially maintained, have also shown that Bcl-2 family proteins are essential in metabolic stress-induced cell death. Glucose deprivation can lead to Bax activation [9,33], and, importantly, Bcl-2 [54–56] or Bcl-xL [5,57,58] expression or deficiency of Bim or Puma [5] can protect cells from apoptosis. Thus, a key initiator of cell death upon loss or inhibition of growth signals is acutely decreased glucose uptake and metabolism that results in activation of pro-apoptotic Bcl-2 family proteins.

Mechanisms linking changes in glucose metabolism to Bcl-2 family proteins after growth factor withdrawal or inhibition of oncogenic kinases are now becoming apparent. Both anti- and pro-apoptotic Bcl-2 family members can respond to changes in glucose metabolism after cytokine withdrawal to promote Bax activation. Cells withdrawn from growth factor demonstrate rapid loss of the anti-apoptotic Bcl-2

protein Mcl-1 [59], due to phosphorylation of Mcl-1 by GSK-3b [4] and subsequent degradation by the proteosome [60,61]. This Mcl-1 degradation pathway is initiated by the acute decrease of glucose metabolism after cytokine withdrawal, as maintenance of glucose metabolism by expression of Glut1 and HK1 inhibits loss of Mcl-1.

Ultimately, reduced Mcl-1 levels allow pro-apoptotic BH3-only proteins, such as Noxa, Bim, and Puma, to promote activation of Bax and Bak [4,5,62]. Of these pro-apoptotic proteins, Noxa does not appear to be directly regulated by cell metabolism, but rather sets a threshold for cell death sensitivity [62]. Bim is strongly induced in response to metabolic stress. Recent work has shown that loss of ATP in the context of neuronal excitotoxicity leads to AMPK-dependent induction of Bim [63], suggesting that Bim induction may be metabolically regulated in certain contexts. However, Bim induction in response to growth factor or glucose withdrawal does not appear to be directly dependent on glucose uptake or metabolism. Rather, Bim is induced by loss of cell signaling [4] or by initiation of endoplasmic reticulum (ER) stress [64]. In contrast, Puma induction is highly sensitive to the loss of cell metabolism, and Puma is unique among pro-apoptotic Bcl-2 family proteins in that its induction is prevented in cells ectopically expressing Glut1 and HK1 [5]. These studies have strongly pointed towards the combined effects of multiple pro-apoptotic Bcl-2 family proteins, along with reduced levels of Mcl-1, in the induction of cell death in the context of decreased glucose uptake.

Although multiple Bcl-2 family proteins contribute to cell death sensitivity, only Mcl-1 and Puma have been shown to directly mediate metabolic stress signaling pathways. As such, these two proteins are

of particular interest in studies examining the direct links between the manipulation of glucose metabolism and the induction of apoptosis. Mcl-1 is well described to have a short half-life [65] and also to be essential to suppress the pro-apoptotic activity of a variety of BH3-only proteins to maintain viability of many primary cells [66–69]. Therefore, metabolic control of Mcl-1 degradation is a primary factor dictating cell survival.

The mechanism of this metabolic sensitivity of Mcl-1 is not entirely certain, but growth factor-driven glucose metabolism appears to alter lipid metabolism to regulate the basal activity of Protein Kinase C (PKC) family kinases. PKC proteins can, in turn, phosphorylate GSK-3b to inhibit GSK-3b-mediated phosphorylation and degradation of Mcl-1 [4]. Conversely, acute loss of glucose metabolism after growth factor or glucose withdrawal may affect lipid profiles and lower PKC activity to decrease inhibitory phosphorylation of GSK-3b and allow Mcl-1 phosphorylation and degradation. PKCs are regulated by lipid binding [70], and changes in cellular lipid profiles in response hyperglycemia have been shown in a number of different cell types [71–73]. Therefore, it is possible that cell intrinsic changes in glucose metabolism may affect lipid levels to influence PKC activity and regulation of GSK-3b. Indeed, the intracellular localization of PKCm and PKCe is altered in cells expressing Glut1 and HK1 [4]. This is consistent with a role for PKCs as sensors of cellular metabolic state, via availability and localization of specific lipids, in the regulation of Mcl-1 stability.

Loss of glucose metabolism after cytokine deprivation also promotes the induction of the BH3-only protein Puma. Puma levels increase in bone-marrow derived cells withdrawn from IL-3, T lymphocytes withdrawn from IL-2, and mast cells withdrawn from a cocktail of cytokine growth factors [5,74,75]. Importantly, upregulation of Puma in this context was suppressed by the maintenance of glucose metabolism in cells expressing Glut1 and HK1 and was essential for rapid cell death, as Puma RNAi strongly attenuated apoptosis of cytokine-deprived cells [5]. Puma is regulated largely at the transcriptional level [76], and growth factor or glucose deprivation led to sharply increased Puma mRNA. While regulation of Puma after cytokine withdrawal has been shown to depend partially on FoxO transcription factors [77], FoxO3a-null cells nevertheless demonstrate induction of Puma and undergo cell death after cytokine withdrawal [74,75,77], suggesting that other transcription factors also play a role as metabolic sensors in the regulation of this Bcl-2 family protein.

In addition to FoxO3a, the tumor suppressor p53 is a key mediator of Puma transcriptional induction. Puma was first identified as a p53 target gene [76,78], and p53-null myeloid progenitor cells and activated T lymphocytes show decreased Puma induction after IL-3 or IL-2 withdrawal, respectively, as compared with wild type cells [5,75]. Recent work has demonstrated that, in addition to the canonical DNA damage response pathway, p53 transcriptional activity increases in the context of cytokine withdrawal [5,75]. The mechanism of this pathway for p53 activation remains unclear. However, the activation of p53 following cytokine withdrawal was suppressed by maintenance of glucose metabolism, suggesting a metabolically-sensitive pathway for p53 activity (Table 1). RNAi knockdown or genetic knockout of p53 prevented Puma induction, demonstrating that the metabolic regulation of Puma is likely mediated through a metabolic checkpoint for p53 activation. A growing number of connections are being established between p53 and cell metabolism [30,79,80], and it appears that a fundamental function of p53 may be to respond to metabolic stress to initiate cell cycle arrest and apoptosis.

4.2. Nutrient limitation

The high rate of glucose uptake in cancerous cells helps to ensure that these cells avoid the stress of nutrient limitation as they continuously grow and divide, but this can occur only when sufficient

nutrients are available. In healthy tissues, the blood supply of nutrients is typically not limiting for basal cell demands. Glucose, glutamine, and oxygen are available well in excess of the amounts required for normal cell metabolism. However, if vascularization fails to meet the needs of growing tissues, such as may occur during development or in rapidly growing solid tumors, or if blood supply is limited to an area due to tissue damage, these nutrients can become restrictive. This is perhaps best appreciated for oxygen limitation, as poorly vascularized tissues can rapidly become hypoxic [81]. However, glucose diffuses through tissue much less efficiently than oxygen, and it too can become limiting as cells compete to consume this resource [82].

While low levels of oxygen, or hypoxia, promote an adaptive transcriptional response through HIF-1 stabilization [83], more severe oxygen depletion constituting anoxia (oxygen levels $\leq 0.5\%$) can induce translocation of Bax from the cytosol to the mitochondrial membrane [84] and apoptosis [46]. This cell death is dependent on activation of pro-apoptotic Bcl-2 family proteins, as expression of Bcl-xL [46] or deficiency of Bax and Bak [85] allow cells to persist even without oxygen. The mechanism that induces activation of Bax and Bak in anoxia is not certain, but the inhibition of mitochondrial oxidative phosphorylation caused by anoxia has been shown to increase proteasomal degradation of Mcl-1 [85]. The loss of this important anti-apoptotic protein, then, may greatly sensitize cells to activation of BH3-only proteins and Bax and Bak.

The roles of BH3-only proteins in anoxia-induced cell death, however, are less well established, as cells null for Bim, Bid, Puma, Noxa, and Bad have all been shown to die at rates similar to that of wild type cells under anoxic conditions [85]. The atypical BH3-only protein BNIP3 has been shown to be upregulated in response to anoxia. However, it remains unclear if BNIP3 plays any role in anoxia-induced cell death, as knockdown of BNIP3 in several cell types failed to protect from anoxic cell death [86]. In contrast, BNIP3-deficiency in neural precursor cells did attenuate cell death in response to the hypoxia mimetic desferrioxamine [87]. A key function of BNIP3 may instead be to facilitate activation of autophagy as an alternate nutrient stress response pathway and metabolic mechanism [88]. This metabolic pathway does, however, ultimately rely on mitochondrial oxidation of lipids and amino acids and, therefore, remains dependent on some oxygen availability. Thus, it remains unclear which BH3-only proteins might respond to the metabolic stress of anoxia to promote cell death or if loss of Mcl-1 alone is sufficient to induce apoptosis.

In contrast to the seemingly limited effects of anoxia on the Bcl-2 family as a whole, limitation of glucose leads to a number of cell stresses that affect multiple Bcl-2 family proteins. Glut1-deficient blastocysts have been shown to activate Bax to induce apoptosis [33,35], and zebrafish lacking Glut1 demonstrate extensive neuronal apoptosis that can be rescued by morpholino-mediated knockdown of Bad [34]. In addition to these in vivo studies, a large amount of work has addressed how cells respond to metabolic stress by examining in vitro glucose deprivation. While this approach leads to a multifaceted cell stress, including metabolic stress, as well as ER stress due to decreased protein glycosylation and defective protein folding [89,90], it is nonetheless useful in providing a broad characterization of how cells respond to these types of injury. Importantly, rescue of metabolism by addition of cell-permeable metabolites, such as methyl-pyruvate or alternative metabolic fuels, can demonstrate that observed effects are due to changes in metabolism rather than to dysregulated protein folding or other non-metabolic consequences of insufficient glucose. Using these approaches, it is now clear that prolonged nutrient deprivation leads to regulation of Bcl-2 family members to induce mitochondrial apoptosis [91], and this occurs independently of ER stress pathways.

Similar to cytokine withdrawal, glucose deprivation leads to increased levels of Bim and Puma [5] and the activation of Bax [9,33]. Cell death is dependent on these proteins, as expression of Bcl-

2 [54–56] or Bcl-xL [5,57,58] or Bim- or Puma-deficiency [5] protects cells from glucose deprivation. However, acute glucose deprivation differs from cytokine withdrawal in that it induces a rapid decrease in intracellular ATP levels [92]. This loss of ATP and the resulting increase in the AMP/ATP ratio can cause the activation of AMP-activated protein kinase (AMPK) [30,93,94], which has been shown to cause cell cycle arrest [30] and reduce Mcl-1 protein levels [62,94] under glucose-limited conditions. Recent work suggests that a block in Mcl-1 translation, caused by AMPK-dependent [94,95] and independent [96] inhibition of mTOR, combined with the short half-life of Mcl-1, causes this loss of Mcl-1 protein that may be critical to sensitize cells to apoptosis [94].

Metabolic regulation of Mcl-1 levels may be particularly important in activated primary T lymphocytes, which primarily utilize glucose and may exhaust glucose availability in inflamed tissues. Noxa can associate tightly with Mcl-1 and is induced during T cell activation. When glucose becomes limiting, Mcl-1 degradation frees Noxa to promote apoptosis [62]. Noxa is somewhat unique among the BH3-only family in that it binds primarily to the anti-apoptotic Bcl-2 proteins A1 and Mcl-1. In healthy Jurkat T cells, a large percentage of total Noxa was found associated with Mcl-1 [62]. Interestingly, however, recent work demonstrated that UV radiation of HeLa cells induced binding between Noxa and Bcl-xL, which was dependent on the loss of Mcl-1, to promote cell death [97]. Thus, changes in Mcl-1 levels upon glucose withdrawal may allow liberated Noxa to bind and inhibit Bcl-xL within activated T lymphocytes, as well, to induce apoptosis.

In addition to affecting the translation of Mcl-1, activation of AMPK upon glucose limitation can also activate the tumor suppressor p53 (Table 1). Under low glucose concentrations, AMPK causes the phosphorylation of p53 on Ser15. While it is not clear if this phosphorylation is direct, it is associated with the induction of p21 and a p53-dependent cell cycle arrest [30]. Complete glucose withdrawal also activates p53 through AMPK, and in this context, AMPK leads to p53 phosphorylation on Ser46 to induce p53-dependent apoptosis [31]. The activation of p53 in the context of glucose withdrawal likely induces cell death through p53-dependent upregulation of Puma, as shRNA-mediated knockdown of p53 attenuates Puma induction in hematopoietic cells cultured without glucose [5]. Furthermore, activated T lymphocytes isolated from p53 knockout mice demonstrate decreased levels of Puma induction after glucose withdrawal [5].

This induction of Puma following glucose withdrawal occurs in response to reduced glucose metabolism specifically, rather than as an indirect effect of other cell stresses caused by glucose limitation. This has been demonstrated by treatment of cells with a cell-permeable form of the glycolytic end-product pyruvate, methyl-pyruvate, which can suppress the increase in Puma levels seen after glucose withdrawal [5]. This effect was independent of ER stress signaling pathways, as the addition of methyl-pyruvate did not alleviate the ER stress caused by glucose withdrawal. Although Puma induction after glucose deprivation is largely p53-dependent [5], it remains unknown how metabolic changes are translated into regulation of Puma protein levels. In particular, it is not yet clear whether mitochondrial metabolism suppresses Puma expression entirely through a transcriptional mechanism involving metabolic control of p53 or FoxO family transcriptional factors, or whether Puma levels are also altered post-translationally, through changes in protein translation or turnover. Given the recent work demonstrating post-translational regulation of Mcl-1 levels after glucose withdrawal, it will be interesting to discover whether the metabolic regulation of Puma involves a similar mechanism.

5. Cell death proteins regulate cell metabolism

Given the complex interplay between cellular metabolism and the induction of apoptosis, it is perhaps not surprising that regulation can occur in the opposite direction as well, with cell death proteins

influencing cellular metabolic status. In addition to its role in promoting cell death, the BH3-only protein Bad is now known to regulate the activity of glucokinase [98]. Bad can localize to the mitochondria as part of a large, multi-protein complex with glucokinase in liver cells [98] and pancreatic b cells [99]. The activity of glucokinase is dependent on the presence of phosphorylated Bad in this complex, as genetic deletion of Bad or the presence of a non-phosphorylatable Bad mutant leads to decreased glucosokinase activity. Furthermore, Bad knockout mice demonstrate impaired glucose tolerance [98], glucose sensing, and glucose stimulated insulin secretion [99]. Thus, the regulation of glucokinase by Bad seems to extend beyond cellular metabolism to metabolic regulation at the organismal level. Interestingly, chronic exposure of pancreatic b cells to high levels of glucose, as might occur with type 2 diabetes, can promote downregulation of glucokinase expression and increased apoptosis [100]. It seems possible that the loss of glucokinase expression may promote apoptosis through release of Bad from its multi-protein complex, which would allow Bad to neutralize anti-apoptotic Bcl-2 family members. Thus, it appears that tight regulation of both metabolic and apoptotic proteins is necessary for proper pancreatic b cell functioning and glucose homeostasis.

Another protein involved in metabolic stress response pathways that is traditionally thought of as apoptotic rather than metabolic is the tumor suppressor p53. As a cell stress-responsive transcription factor, p53 exerts many of its effects through regulation of a variety of target genes. Emerging data now demonstrate that p53 has additional fundamental functions, beyond its roles in genomic repair, cell cycle progression, and apoptosis, which include the regulation of cellular metabolism. The p53 target gene synthesis of cytochrome c oxidase 2 (SCO2) is required for assembly of the mitochondrial cytochrome c oxidase complex and is therefore necessary for mitochondrial respiration. Cells deficient in p53 signaling have decreased levels of SCO2 and mitochondrial oxygen consumption and compensatory increased rates of glycolysis [80]. Additionally, p53 is known to downregulate expression of the glycolytic enzyme phosphoglycerate mutase (PGM) [101] and upregulate the expression of TIGAR (TP53-induced glycolysis and apoptosis regulator) [79]. TIGAR decreases levels of fructose-2,6-bisphosphate (Fru-2,6-P_2). Fru-2,6-P_2 allosterically activates the glycolytic enzyme phosphofructokinase. Thus, p53-mediated regulation of both PGM and TIGAR serve to lower glycolytic flux and can instead direct glucose into the pentose phosphate shunt to help control reactive oxygen species [79].

Interestingly, given the anti-apoptotic effects of increased glycolysis described above, these p53-mediated changes in glucose metabolism seem to fall in line with p53's role as a tumor suppressor. In combination with its ability to induce expression of BH3-only proteins, including Bax, Puma, and Noxa, p53 may also promote apoptosis by decreasing glycolytic rates to relieve the anti-apoptotic effects of glycolysis. The importance of p53's role in regulating cell metabolism also becomes apparent when considering that the majority of cancerous cells demonstrate dysfunctional p53 signaling that may enhance aerobic glycolysis. This regulation of cell metabolism and links between cell metabolism and apoptosis may thus reflect an additional and generally underappreciated way in which inactivation or mutation of p53 in cancer cells may enhance cancer progression.

6. Targeting metabolism in cancer therapy

Given the findings described above demonstrating intricate links between cellular metabolism and cell fate, the prospect of targeting cellular metabolism in cancer seems particularly attractive. The high frequency with which cancer cells arising from different cell types adopt a Warburg-like metabolic program suggests that a glycolytic metabolism is highly beneficial to tumor growth. Therefore, decreasing glycolysis within tumor cells, or driving them back into an

oxidative metabolic program, may represent a viable strategy not only to reduce cell growth, but also to induce apoptosis. Indeed, the very signaling pathways that can mediate transformation, such as the PI3K/Akt pathway, also promote increased glycolysis and may make cancer cells particularly sensitive to therapies that target glucose metabolism. Akt both promotes aerobic glycolysis and also phosphorylates CPT1A to inhibit lipid transport into mitochondria [26], thus forcing cells with activated Akt to rely heavily on glucose as a fuel source. Similarly, Myc can promote the expression of genes involved in glutamine metabolism and renders cells highly dependent on this amino acid as a mitochondrial fuel.

The molecular connections between metabolism and Bcl-2 family proteins represent the most direct means to exploit cell metabolism in cancer and potentially develop new, more effective treatment strategies. However, metabolism occurs within every cell in the body and is essential to the maintenance of homeostasis. Thus, despite the tremendously increased rates of glucose uptake and glycolysis seen in cancerous cells and the large amount of data detailing the links between metabolism and apoptosis, effective therapies that specifically target tumor metabolism have remained elusive. It would seem that two potential strategies for such treatments exist, one that attempts to directly target the metabolic pathways themselves and another targeting the proteins that regulate cell metabolism.

Regarding the first strategy, it is now apparent that manipulation of aerobic glycolysis can impact proliferation and survival in cancer cells. Forcing cells to shift from a glycolytic to a more oxidative metabolic program may slow tumor growth. Inhibition of lactate dehydrogenase A, via shRNA-mediated knockdown, increases mitochondrial respiration and inhibits cell proliferation in cell culture experiments and in mouse xenograft models, where resulting tumors were small and necrotic [102]. Similarly, treatment with dichloroacetate shifts cells toward oxidative metabolism, through inhibition of mitochondrial pyruvate dehydrogenase kinase, and induces cytochrome c release from the mitochondria and apoptosis in cancer cells [103]. Additionally, inhibition of glucose metabolism may be an effective means of halting tumor growth, as pharmacologic suppression of PFK activity has been shown to decrease glucose uptake and impair cancer cell proliferation, both in vitro and in vivo [104].

Moreover, treatment with the glycolysis inhibitor 2-deoxyglucose (2-DOG) enhances cisplatin-induced cell death in ovarian cancer cells [105] and induces apoptosis in prostate cancer cells when used in combination with the AMPK activator metformin [106]. Perhaps not surprisingly, combining multiple metabolic stresses, by treating cells with 2-DOG in the context of hypoxia, has been shown to enhance cell cycle arrest and cell death above that seen in normoxic cells treated with 2-DOG [107]. This is thought to reflect the fact that hypoxic cells, unable to produce ATP via oxidative phosphorylation, rely more heavily on glycolytic metabolism. These findings imply that the addition of glycolysis inhibitors to traditional chemotherapeutic agents may enhance efficacy, by targeting cells within hypoxic portions of solid tumors that might proliferate more slowly and thus resist chemotherapies targeting proliferating cells.

Interestingly, inhibition of glucose metabolism may concurrently protect healthy cells from chemotherapy-induced cell death [108,109]. It may be that glucose limitation induces a p53-dependent cell cycle arrest in healthy cells expressing wild type p53 [30], allowing these cells to arrest and avoid the cytotoxic effects of chemotherapy. In contrast, p53-null tumor cells may continue to proliferate and consequently be susceptible to traditional chemotherapeutic agents. This would also suggest that p53-null cancer cells might be more sensitive to metabolic manipulation than cancer cells retaining wild type p53. However, inhibition of glucose metabolism can also induce p53-dependent apoptosis [31], and cells lacking functional p53 have been shown to resist caspase activation after combination treatment with 2-DOG and metformin [106]. Thus, the

induction of apoptosis by metabolic manipulation, and the role of p53 in this process, may be cell type- or context-dependent.

While inhibition of metabolic enzymes and pathways shared between normal and cancerous tissue is challenging, it is now clear that cancer cells can express specific isoforms or mutations of metabolic enzymes that may be directly targeted to exploit cancer cell metabolism specifically. Mutations in two isoforms of isocitrate dehydrogenase (IDH), IDH1 and IDH2, have been identified in a large percentage of certain types of malignant gliomas and in acute myelogenous leukemia [110–112]. IDH1, which is found in the cytosol, and IDH2, located in the mitochondria, exist as homodimers and catalyze the conversion of isocitrate to a-ketoglutarate in a $NADP^+$-dependant reaction [113]. Mutant forms of both IDH1 and IDH2 have been shown to decrease the rate of this reaction and to catalyze instead the conversion of a-ketoglutarate to 2-hydroxyglutarate (2-HG), which accumulates to very high levels within IDH-mutant cells [114–116]. While the functional effects of this metabolic alteration remain unknown, targeting of this cancer specific, mutant enzyme, or the 'oncometabolite' that it produces, represents a potentially attractive therapeutic strategy.

Also of interest is the altered expression in cancerous cells of the glycolytic enzyme pyruvate kinase, which converts phosphoenolpyruvate to pyruvate in the rate-limiting final step of glycolysis. While most differentiated adult tissues express the M1 isoform of pyruvate kinase (PKM1), proliferating cells, including cancer cells, almost exclusively express the M2 isoform (PKM2) [117]. Expression of PKM2 promotes aerobic glycolysis over oxidative metabolism, and this metabolic switch seems to be important for tumor formation, as forced expression of PKM1 suppresses tumor growth in vivo [117]. Interestingly, within tumor cells, PKM2 is typically found in its less active, dimeric form [118], and the activity of PKM2 may be further suppressed by binding to phosphotyrosine peptides [119] found in abundance in cancer cells. In this scenario, the high rates of glucose uptake in cancer cells are accompanied by suppression of the final step of glycolysis. The advantage to this seemingly paradoxical pattern, however, is that glycolytic intermediates upstream of pyruvate accumulate and can be used as precursors for macromolecular synthesis. In addition, glucose flux through the pentose phosphate pathway may increase to enhance protection against reactive oxygen species. These finding suggest that targeting of PKM2 in cancer may represent a viable strategy.

A second possible method for targeting cancer metabolism to promote apoptosis is to attack the master regulators of cell metabolism that control the switch to aerobic glycolysis. A number of molecularly targeted therapies have now been developed against oncogenic tyrosine kinases, such as Her2/neu, EGFR, and Bcr-Abl. By inhibiting signaling downstream of these kinases, these therapies indirectly target the PI3K/Akt pathway, and many effectively suppress glucose uptake and metabolism [50,120–122]. Additionally, a number of PI3K inhibitors are now in phase I and II clinical trials. Whether these therapies can effectively target such a universally used pathway without significant toxicities remains to be seen. However, preclinical trials have noted only mild side effects, which predictably included metabolic disturbances and elevated blood glucose levels [123].

Other potential targets include transcription factors that orchestrate metabolic changes. Myc inhibition appears to hold potential based on cell culture assays and animal model experiments [124–126], although this strategy has not yet been tried in patients. Nuclear receptors represent another class of transcription factors known to play a large role in the regulation of cell metabolism. The estrogen receptor, in particular, has been successfully targeted for the treatment of breast cancer, demonstrating the drugability of these proteins. Other nuclear receptors, such as the PPARs [127] and estrogen related receptors [128,129], regulate multiple aspects of cell metabolism. However, a role for these proteins as cancer therapeutic targets remains to be established.

7. Conclusion

The metabolic status of a cell is intimately tied to its ability to successfully grow, proliferate, and survive. If nutrients or metabolic pathways are not sufficient for these processes, growth factor stimulation or oncogenic transformation cannot mediate their effects. Thus, it is not surprising that apoptotic regulatory proteins are closely associated with cell metabolism and the mitochondria. This system allows Bcl-2 family proteins to initiate apoptosis in metabolically stressed cells, rather than allowing cells to survive for prolonged periods of time through utilization of autophagy as a nutrient source before ultimately undergoing necrosis [130]. The molecular pathways that connect metabolism to Bcl-2 family proteins are just beginning to come into focus, but given the fundamental role of cell metabolism in regulating cell fate, these mechanisms will be of great interest in a variety circumstances. In particular, strategies to kill cancer cells by exploiting metabolic addiction may benefit from an increased understanding of which metabolic stress pathways are most closely linked to the induction of apoptosis by the Bcl-2 family.

Acknowledgements

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