Therapeutic Targeting of Myc-Reprogrammed Cancer Cell Metabolism

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Studies from many laboratories document that the MYC oncogene produces a pleiotropic transcription factor, Myc, which influences genes driven by all three RNA polymerases to orchestrate nutrient import with biomass accumulation for cell division. Myc has been shown to activate genes involved in glycolysis, glutaminolysis, and mitochondrial biogenesis to provide ATP and anabolic substrates for cell mass accumulation. Myc stimulates ribosome biogenesis and orchestrates the energetic demand for biomass accumulation through its regulation of glucose and glutamine import and metabolism. When normal cells are deprived of nutrients, endogenous MYC expression diminishes and cells withdraw from the cell cycle. However, ectopic MYC-driven cancer cells are locked in a state of deregulated biomass accumulation, which renders them addicted to glucose and glutamine. This addictive state can be exploited for cancer therapy, because nutrient deprivation kills Myc-driven cells and inhibition of the Myc targets, lactate dehydrogenase A or glutaminase, diminishes tumor xenograft growth in vivo.

Our perspectives of cancer biology have been framed by extant technologies and evolving conceptual frameworks. Molecular biology emerged in the 1970s and profoundly transformed our understanding of the causes of cancer through the discoveries of oncogenes, tumor suppressors, and mutator genes. Alteration in cancer cell metabolism, however, was met with skepticism that portrayed these alterations as epiphenomena. Specifically, the Warburg effect or the propensity of cancer to convert glucose to lactate in aerobic conditions (aerobic glycolysis) has been dismissed and only recently considered as an emerging hallmark of cancer, despite having been described almost 90 years ago (Hanahan and Weinberg 2011; Koppenol et al. 2011). It is now untenable to deny an intimate or causal role of altered metabolism in the development and maintenance of cancers. Specifically, mutations in enzymes such as succinate dehydrogenase, fumarate hydratase, and isocitrate dehydrogenase have been linked to familial and sporadic human cancers (Frezza et al. 2011). Furthermore, virtually all oncogenes and tumor suppressors are linked to metabolic pathways (Cairns et al. 2011). In fact, oncogenes such as Ras, Src, and Myc were linked to metabolism in the 1980s and 1990s, with Myc documented as a transcriptional factor that directly activates the lactate dehydrogenase A (LDHA) gene, thereby conferring the Warburg effect (Cooper et al. 1983; Flier et al. 1987; Shim et al. 1997). It should be noted, however, that the growth of a cancer cell, or any cell for that matter, requires more than just glucose and ATP (Brand 1985; Newsholme et al. 1985; Deberardinis et al. 2008; Vander Heiden et al. 2009). Cells are not composed of just carbon, hydrogen, and oxygen; nitrogen, phosphorus, sulfur, minerals, and vitamins are also required for cell growth or biomass accumulation. Hence, it is not particularly

surprising that, in addition to glucose, glutamine has been known for 55 years as an essential ingredient for cultured cells to proliferate (Eagle 1955; Newsholme et al. 1985).

MYC ONCOGENE

The MYC oncogene, which produces the Myc transcription factor, has emerged as a master regulator of metabolism for cell growth and proliferation (Eilers and Eisenman 2008). MYC (c-myc) belongs to a family of related human genes including MYCN (N-myc) and MYCL (L-myc), which evolved from primordial Myc-like genes found in *Drosophila* and *Hydra* (Hartl et al. 2010). Myc is essential for murine embryogenesis, which is programmed for rapid cell proliferation (Davis et al. 1993; de Alboran et al. 2001). Upon terminal cell differentiation, Myc expression is diminished such that ectopic Myc expression is sufficient to block differentiation (Prochownik and Kukowska 1986; Freytag et al. 1990). Somatic differentiated cells, however, can be reprogrammed by Sox2, Oct4, KLF4, and MYC into a pluripotent stem cell state, attesting to the plasticity of the differentiated cellular genome (Takahashi and Yamanaka 2006). MYC is an early response gene with growth factor stimulation, such that its expression is diminished when normal tissue stem cells return to a nonproliferative, homeostatic state (Kelly et al. 1983). In the absence of nutrients, normal cells do not proliferate and cultured cell populations return to G₀ or G₁, a resting phase of the cell cycle. In contrast, when MYC is oncogenically activated—for example, by chromosomal translocation or gene amplification—its deregulated expression switches cancer cells into a constitutive state of biomass accumulation, a condition addictive to nutrients (Shim et al. 1998; Yuneva et al. 2007; van Riggelen et al.

2010). The addictive state of a Myc-driven cancer cell provides a therapeutic window for targeting cancer cell metabolism.

MYC, RIBOSOME BIOGENESIS, AND BIOMASS ACCUMULATION

Because Myc functions as a transcription factor by heterodimerizing with Max to regulate cell growth and proliferation, the genomics of Myc target genes has been an area of intense interest. Many laboratories have contributed to the picture that Myc activates and represses thousands of genes that are regulated by RNA polymerases I, II, and III (White 2005; Eilers and Eisenman 2008). Given its broad reach, it stands to reason that Myc is like a conductor of a symphony for cell growth and proliferation, orchestrating genes driven by all three RNA polymerases (Dang 2010). Clues for Myc's primordial function came from fly genetics, which revealed that a natural hypomorph allele of dMyc results in small cells and small body size of the diminutive mutant *Drosophila* that phenocopies flies with loss of function of ribosomal protein genes (Gallant et al. 1996; Johnston et al. 1999). In this regard, Myc is also documented to directly regulate rRNA synthesis, nucleotide biosynthesis, as well as ribosomal protein genes (Bello-Fernandez et al. 1993; Kim et al. 2000; Eberhardy and Farnham 2001; Nikiforov et al. 2002; Arabi et al. 2005; Grandori et al. 2005; Liu et al. 2008). Furthermore, a search for a cell type-independent Myc core target gene signature has revealed a 50-gene signature that is highly enriched for genes involved in RNA processing and ribosomal biogenesis (H. Ji et al. unpubl.). Hence, the primordial function of Myc is to regulate ribosomal biogenesis, a process that is bioenergetically demanding, particularly because ribosomes constitute the bulk of cellular dry mass (Fig. 1).

Given that ribosomes are a major constituent of cells, microbial eukaryotes such as the yeast *Saccharomyces cerevisiae* must have a means of linking nutrient sensing to ribosome biogenesis (Lempiäinen and Shore 2009). Indeed, glucose and glutamine sensing have been linked via Ras and Torc pathways in budding yeast to the regulation of Ribi (ribosome protein) genes. Mutations in these pathways that render constitutive Ribi gene expression cause mutant yeasts to be less viable in the absence of glucose or glutamine, in essence causing them to be addicted to nutrients (Lippman and Broach 2009). In mammalian cells, rRNA synthesis is sensitive to glucose

deprivation, which inactivates the Pol I transcription factor TIF-1A via AMPK-mediated phosphorylation (Hoppe et al. 2009). Furthermore, the rise in NAD^+ with glucose deprivation stimulates SIRT1, which is a component of the rDNA (DNA coding for rRNA) chromatin silencing complex termed eNoSC (energy-dependent nucleolar silencing complex) that cloaks rDNA chromatin from being read by the transcriptional machinery (Murayama et al. 2008). Because energy status is linked to ribosome biogenesis and Myc regulates ribosome biogenesis, Myc must also regulate nutrient availability for the cell.

MYC STIMULATION OF GLUCOSE AND GLUTAMINE METABOLISM

Lactate dehydrogenase A was identified as a direct Myc target gene via subtraction cloning of genes that were differentially expressed between control cells and those overexpressing Myc (Shim et al. 1997). Subsequently, Myc was documented to directly activate virtually all glycolytic enzyme genes, many of them through phylogenetically conserved Myc binding sites (5'-CACGTG-3') or E-boxes (Osthus et al. 2000; Kim et al. 2004). Deregulated Myc binds to E-boxes that are shared with the hypoxia-inducible factor 1 (HIF-1), and the two factors could occupy overlapping sites in hypoxia, suggesting that Myc drives aerobic glycolysis and contributes to the Warburg effect whereas normal HIF-1 stimulates anaerobic glycolysis for cellular adaptation to hypoxia (Kim et al. 2006, 2007). In this regard, it is notable that the E-box is one of the most abundant *cis*-element motifs found in the human genome (Xie et al. 2005). Since many E-box binding proteins (SREBP, ChREBP, HIF, NRF1, and Clock-Bmal) regulate genes involved in specific aspects of cellular metabolism for homeostasis of nonproliferating cells, one could surmise that Myc can commandeer E-box-driven genes in proliferating cells to coordinate nutrient uptake with lipogenesis, mitochondrial biogenesis, and biomass accumulation (Fig. 1).

With Myc's ability to stimulate glycolysis in aerobic conditions, which contrasts with HIF-1's activation of glycolysis under anaerobic conditions, it stands to reason that Myc might also regulate mitochondrial production and function. In this regard, Myc was documented to regulate many NRF-1-regulated mitochondrial genes and specifically to stimulate mitochondrial biogenesis

Figure 1. Myc regulates genes involved in lipogenesis, ribosome biogenesis, glycolysis, and glutaminolysis. The Myc–Max heterodimeric transcription factor is shown bound to an E-box along with another anonymous transcription factor (TFi), and both regulate genes involved in lipogenesis, nucleotide, and protein synthesis. Myc also regulates genes involved in glucose and glutamine metabolism to provide ATP and anabolic substrates for biomass accumulation.

(Morrish et al. 2003; Li et al. 2005; Kim et al. 2008; Ahuja et al. 2010). Furthermore, a potent direct Myc target PGC1 β , a cofactor for mitochondrial biogenesis, was shown to be necessary for the Myc-induced increase in mitochondrial mass (Zeller et al. 2006; Zhang et al. 2007). Myc also alters the mitochondrial proteome by increasing the levels of a number of proteins, including mitochondrial glutaminase (Gao et al. 2009). These observations suggest that, in addition to regulation of glycolysis, Myc must also regulate glutamine metabolism. In fact, Myc directly regulates a key glutamine transporter gene (SLC1A5 or ASCT2) as a direct target. However, glutaminase (GLS) protein levels are elevated through Myc's repression of miR-23a and miR-23b, which targets the 3' UTR of the GLS mRNA. An E-box is also found in the GLS promoter, suggesting that Myc could also directly regulate GLS (Wise et al. 2008). Collectively, these observations indicate that Myc can couple biomass accumulation with the increased utilization of nutrients such as glucose and glutamine through transcriptional or posttranscriptional mechanisms mediated by miRNAs.

DEREGULATED MYC EXPRESSION AND NUTRIENT ADDICTION

The genomics of Myc target genes indicates that Myc is involved in the regulation of glucose and glutamine metabolism as well as ribosomal biogenesis, suggesting a unifying conceptual framework for Myc function.

Normal cells capable of proliferation can be stimulated by growth factors to enter into the cell cycle following activation of the MYC proto-oncogene. Upon stimulation, a program elicited by the Myc transcription factor activates genes that increase the import of glucose, glutamine and other nutrients as well as those involved in lipogenesis, nucleotide biosynthesis, mitochondrial and ribosomal biogenesis. The bioenergetic needs of the biosynthetic machineries are met by a commensurate amount of bioenergetic and anabolic substrates. When a critical cell mass is reached, the cell is prepared to protect the genome in S phase as it is being replicated for the next generation. If extracellular signals return to basal homeostatic levels, these cells return to a resting phase, G₁. In the case of a cancer cell driven by Myc, much like a yeast mutant rendered constitutive for ribosomal biogenesis, the continuous need for bioenergetics to support deregulated biomass accumulation causes oncogene-driven cells to be addicted to nutrients such as glucose or glutamine (Shim et al. 1998; Yuneva et al. 2007; Lippman and Broach 2009). Evidence that Myc-driven cells are addicted to glucose was documented by the observation that glucose-withdrawal induced apoptosis in a number of Myc-overexpressing cells (Shim et al. 1998). Likewise, Myc-overexpressing human cells are quite sensitive to glutamine withdrawal as compared with control cells (Yuneva et al. 2007). In this regard, it can be surmised that critical metabolic nodes involved in metabolism could be targeted in Myc-driven (or other deregulated oncogenes that drive constitutive biomass accumulation) tumors for cancer therapy (Fig. 2).

Figure 2. Myc regulation of glucose and glutamine metabolism is coupled with its induction of biomass accumulation. Normal cells retreat into a quiescent state when deprived of nutrients, in contrast to ectopic Myc-driven cells that are addicted to glucose or glutamine. The diagram illustrates the need for bioenergetic support of biomass accumulation and a commensurate bioenergetic supply provided by glycolysis and glutaminolysis. Glucose is shown imported and converted to pyruvate by glycolysis. Pyruvate is then largely converted by lactate dehydrogenase A (LDHA) to lactate with some being converted to acetyl-coenzyme A for catabolism in the tricarboxylic acid (TCA) cycle. TCA cycle intermediates are shown with α -ketoglutarate depicted as a hub for the entry of glutamine, which is converted by glutaminase (GLS) to glutamate, into the TCA cycle. Tool compounds targeting LDHA or GLS have provided proof of concept that targeting metabolism is feasible.

TARGETING LDHA AND GLS FOR CANCER THERAPY

With LDHA documented in 1997 as a direct Myc target, LDHA expression was diminished by antisense RNA expression to determine its potential importance in tumorigenesis and tumor maintenance (Shim et al. 1997). The suppression of LDHA expression was sufficient to diminish in vitro transformed phenotypes such as soft agar clonogenicity of human Burkitt lymphoma cells. Subsequently, unpublished work (H Shim and C Dang) showed that these same cells were unable to establish xenograft tumors in nude mice. These early observations have been corroborated and significantly advanced by five independent studies that used shRNA to target LDHA expression in different tumor xenograft models (Fantin et al. 2006; Xie et al. 2009; Le et al. 2010; Qing et al. 2010; Seth et al. 2011; Wang et al. 2011). Furthermore, proof of concept for targeting LDHA pharmacologically was provided by evidence that FX11, a low micromolar inhibitor of LDHA, was capable of inhibiting in vivo lymphoma progression (Le et al. 2010). Collectively, these observations indicate that specific targeting of glycolysis in Myc-driven cancer models can result in cancer control (Fig. 2).

The observation that a nontoxic dose of FX11 could control the increase in tumor size but could not cause tumor reduction suggests that glutamine metabolism could compensate for the interruption of glucose metabolism. In this regard, it would be of great interest to gain a richer understanding of glutamine metabolism in aerobic and hypoxic conditions, which are generally found in tumor tissues. Using uniformly ^{13}C , ^{15}N -labeled glutamine with NMR and GC-MS analyses in unpublished studies (A Le et al.), glutamine was found to contribute to TCA cycle intermediates in aerobic conditions and unexpectedly under hypoxic conditions when Myc is activated. These observations suggest that ongoing hypoxic glutamine metabolism is essential for Myc expressing cells, such that either siRNA knockdown of GLS or pharmacological inhibition of GLS with a small molecule, BPTES (*bis*-2-[5-phenylacetamido-1,2,4-thiadiazol-2-yl]ethyl sulfide), resulted in decreased aerobic cell proliferation and hypoxic cell death (Robinson et al. 2007). These observations indicate that targeting GLS is reasonable, and in fact an inhibitor, 968 (unrelated to BPTES), of GLS proved as a single agent to decrease lymphoma xenograft growth (Wang et al. 2010). In unpublished work (P Gao, R Dinavahi, and C Dang), BPTES was also found to be effective in diminishing lymphoma xenograft growth (Fig. 2).

CONCLUDING REMARKS

In conclusion, Myc emerges in a unified model of its function as a pleiotropic transcription factor that can stimulate the transcription of a wide range of E-box-driven genes, which are otherwise regulated by other E-box transcription factors under nonproliferative conditions. These E-box-driven genes are involved in lipogenesis,

carbohydrate metabolism, glycolysis, mitochondrial biogenesis, and redox homeostasis. When their expression is coordinated by Myc with genes involved in ribosomal biogenesis and nucleotide biosynthesis that are uniquely driven by Myc rather than the homeostatic E-box transcription factors, the cell could utilize bioenergetics and anabolic substrates to build cellular mass for cell replication. When Myc is deregulated, the addictive need for nutrients driven by constitutive biomass accumulation provides a therapeutic window that could be exploited for cancer therapy by targeting specific enzymes such as LDHA or GLS.

Because Myc is only one of many oncogenes and tumor suppressors that have been directly linked to metabolic pathways, a richer understanding of these connections in the next few years will likely reveal additional metabolic nodes that could be exploited for cancer therapy. It is surmised that genetic alterations in cancers are hard-wired to metabolic pathways such that different cancers may have characteristic reprogrammed metabolic networks, which could be strategically targeted over the next few years.

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