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MYC and Mitochondrial Biogenesis

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Mitochondria, the powerhouses of the cell, face two imperatives concerning biogenesis. The first is the requirement for dividing cells to replicate their mitochondrial content by growth of existing mitochondria. The second is the dynamic regulation of mitochondrial content in response to organismal and cellular cues (e.g., exercise, caloric restriction, energy status, temperature). MYC provides the clearest example of a programmed expansion of mitochondrial content linked to the cell cycle. As an oncogene, MYC also presents intriguing questions about the role of its mitochondrial targets in cancer-related phenotypes, such as the Warburg effect and MYC-dependent apoptosis.

Once a consensus DNA-binding site for MYC was identified, transcriptional targets of MYC began to be identified (Blackwell et al. 1990). Early efforts led to the discovery of several nuclear-encoded mitochondrial genes as MYC targets. One of the first recognized mitochondrial targets of MYC, SURF-1 is a serum-regulated complex IV assembly factor that lacks an E-box MYC-binding site in its promoter (Vernon and Gaston 2000). MYC activity at the SURF-1 promoter requires the transcription factor YY1 and its cognate binding site. YY1 regulates the expression of multiple COX subunits (Seelan and Grossman 1997) and possibly other mitochondrial proteins based on binding-site analysis (Xi et al. 2007) and has been shown to interact with MYC (Shrivastava et al. 1996).

The advent of oligonucleotide-based microarrays enabled a more intensive approach to discovery of MYC-regulated genes. Early efforts identified 18 mitochondrial genes up-regulated by MYC, including cytochrome *c* (Coller et al. 2000; Guo et al. 2000; Neiman et al. 2001; Schuhmacher et al. 2001).

A mitochondrial peroxiredoxin, PRDX3, was subsequently shown to be directly regulated by MYC binding to sites within the promoter and first intron containing canonical and noncanonical E boxes (Wonsey et al. 2002). Peroxiredoxins function as thioredoxin-dependent peroxide reductases. Antisense-mediated suppression of PRDX3 expression diminished mitochondrial membrane potential and mass. PRDX3 expression in fibroblasts was required for maximal MYC-dependent proliferation, nonadherent growth, and tumorigenesis. Notably, PRDX3 was also required for apoptosis of MYC-expressing cells upon withdrawal of glucose, but not serum. A mitochondrial chloride channel required for MYC-dependent apoptosis, CLIC4, was also reported to be a direct MYC target (Shiio et al. 2006).

An analogous finding of a mitochondrial factor required for MYC-dependent cell growth

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is provided by the mitochondrial serine hydroxymethyltransferase (SHMT2) gene. A cDNA library enriched in MYC-responsive cDNAs was screened for restoration of the growth defect in *MYC*-null cells (Nikiforov et al. 2002). The only reproducible increase in cell proliferation was observed with SHMT2. Chromosomal immunoprecipitation analysis revealed that MYC binds to an E-box-containing SHMT2 promoter sequence. SHMT enzymes convert serine and tetrahydrofolate to glycine and 5,10-methylene tetrahydrofolate, a key reaction in one-carbon metabolism. In addition to the importance of folate cofactors as methyl donors, rapidly proliferating cancer cells show a high requirement for glycine, which is used in purine and heme biosynthesis (Jain et al. 2012).

GLOBAL ASSESSMENTS OF THE MYC-REGULATED MITOCHONDRIAL TRANSCRIPTOME

The most comprehensive analyses of mitochondrial targets of MYC to date identified 400 nuclear genes encoding mitochondrial proteins, out of 7054 genes identified as MYC targets by chromosomal immunoprecipitation analysis of promoter microarrays, and 198 out of 1578 genes induced by ectopic MYC expression (Kim et al. 2008a; Seitz et al. 2011). Included are major categories of genes involved in bigenomic and mitochondrial transcription, mitochondrial translation, protein import, and complex assembly (Fig. 1). A direct comparison of ectopic and endogenous MYC expression showed a high concordance, supporting a physiological role for MYC in mitochondrial biogenesis (Li et al. 2005). An up-to-date compilation at the time of this review identified 599 nuclear genes encoding mitochondrial proteins (out of 1598 nuclear genes in the current MitoExome) (Lieber et al. 2013) as downstream targets of MYC, based on RNA expression or direct DNA binding (Table 1). MYC also indirectly regulates mitochondrial gene expression via repression of microRNAs controlling nuclear genes encoding mitochondrial proteins (e.g., miR-23a/b and glutaminase) (Gao et al. 2009; Psathas and Thomas-Tikhonenko 2014).

A published analysis of mitochondrial gene expression in the NCI-60 cell line panel found that MYC expression positively correlated with expression levels of 15.7% of mitochondrial nuclear-encoded genes, and negatively correlated with 1.9% (Zoppoli et al. 2011). For comparison, MYC was positively correlated with 12.6% of nonmitochondrial genes.

OVERVIEW OF MITOCHONDRIAL BIOGENESIS

Mitochondrial biogenesis is primarily regulated at the transcriptional level, with a limited number of transcription factors orchestrating the synthesis of the more than 1000 nuclear-encoded mitochondrial proteins and 13 proteins encoded by mtDNA. NRF-1 was identified through binding to a conserved site in the cytochrome *c* promoter and subsequently shown to regulate multiple mitochondrial genes including oxidative phosphorylation complex subunits, protein import and assembly factors, and ribosomal proteins (Kelly and Scarpulla 2004). The mtDNA replication and transcription factors Tfam, Tfb1m, and Tfb2m are also NRF-1 targets. NRF-$1^{-/-}$ blastocysts have reduced mtDNA and low mitochondrial membrane potential, but targeted overexpression in muscle does not increase respiratory capacity, suggesting that NRF-1 is necessary but not sufficient for mitochondrial biogenesis (Huo and Scarpulla 2001; Baar et al. 2003). Functional NRF-1-binding sites are also found in genes involved in DNA replication, cytokinesis, and mitosis, including many E2F-regulated genes (Cam et al. 2004). Certain noncanonical E-box sites bound by MYC match binding sites for NRF-1, suggesting that some of the overlapping targets may contain dual NRF-1/MYC recognition sites. In the case of cytochrome *c*, MYC binding to a promoter sequence and transcriptional activity in reporter assays require an intact NRF-1 site (Morrish et al. 2003).

GA-binding protein (GABP), also known as NRF-2, is an Ets-domain-containing tetrameric transcription factor identified through binding to the COX IV promoter. Recognition sites for GABP often occur with NRF-1-binding sites in

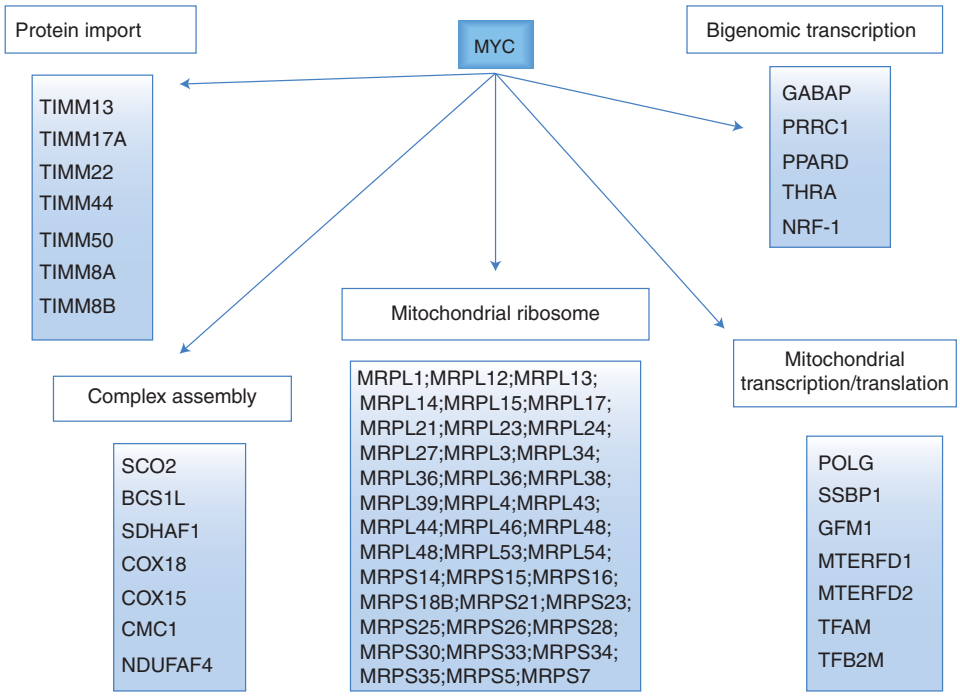

Figure 1. Examples of direct MYC target genes involved in mitochondrial biogenesis. Derived from ChIP-seq data from five Burkitt lymphoma cell lines (Seitz et al. 2011).

the same promoter (Kelly and Scarpulla 2004). GABP is also required for hematopoietic cell self-renewal and normal T-cell development (Yu et al. 2010, 2012).

Estrogen-related receptors α and β were the first identified nuclear orphan receptors (Giguere et al. 1988). Based on crystal structures of the ERR-α and -γ ligand-binding domains, transcriptional activity of these factors is possibly ligand-independent (Grischik et al. 2002). ERRs interact with several coactivators or protein ligands, most notably PPAR-γ coactivators (PGC)-1α and PGC-1β (Huss et al. 2002). In addition to mitochondrial biogenesis, ERRs regulate fatty acid oxidation, the TCA cycle, oxidative phosphorylation, transcription/translation, and transporters, covering an estimated one-half of the mitochondrial proteome (Giguere 2008).

The peroxisomal proliferator-activated receptors (PPAR-α, -γ, -δ) were the first nuclear receptors identified with mitochondrial metabolism genes as transcriptional targets. These receptors have incompletely characterized lipid ligands and regulate lipid metabolism, including mitochondrial fatty acid oxidation. They are required for adaptive thermogenesis, ketogenic responses to fasting, and adipocyte and skeletal muscle oxidative fiber type differentiation, while indirectly promoting mitochondrial biogenesis in specific tissues such as white adipose tissue, skeletal muscle, and alternatively activated macrophages (Wilson-Fritch et al. 2003). PPAR receptors also led to the discovery of the PPAR-γ coactivators. PGC-1α, PGC-1β, and PRC (PGC-1-related coactivator) function as coactivators for ERRs, NRF-1, and GABP, in addition to PPARs, through leucine-rich and other protein interaction motifs. These coactivators recruit CBP/p300 and Mediator-associated histone acetyltransferases to enhance transcription initiation and elongation in a coordinated program of mitochondrial biogenesis (Handschin and Spiegelman 2006). Multiple types of posttranslational modification (phosphorylation, acetylation, arginine methylation) regulate PGC-1α function.

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Table 1. Nuclear-encoded mitochondrial gene downstream targets of MYC

AARS2 (Seitz et al. 2011)
AATK (Seitz et al. 2011)
ABCB10 (Li et al. 2005; Seitz et al. 2011)
ABCB6 (Li et al. 2003; Kim et al. 2008a; Seitz et al. 2011)
ABCB8 (Kim et al. 2008a)
ABCE1 (Ji et al. 2011)
ABCF2 (Li et al. 2005; Seitz et al. 2011)
ACAA2 (Kim et al. 2008a)
ACAD8 (Li et al. 2003)
ACAD9 (Morrish et al. 2008; Seitz et al. 2011)
ACADM (Fernandez et al. 2003)
ACADVL (Kim et al. 2008a)
ACAT1 (O'Connell et al. 2003; Zeller et al. 2006)
ACBD3 (Kim et al. 2008a)
ACN9 (Zeller et al. 2006; Seitz et al. 2011)
ACO2 (Fernandez et al. 2003; Kim et al. 2008a)
ACOT13 (Morrish et al. 2008)
ACOT7 (Ji et al. 2011; Seitz et al. 2011)
ACSF3 (Seitz et al. 2011)
ACSL1 (Morrish et al. 2008; Seitz et al. 2011)
ACSL5 (Seitz et al. 2011)
ACSM3 (Seitz et al. 2011)
ACSS1 (Zeller et al. 2006)
ADC (Seitz et al. 2011)
ADCK3 (Li et al. 2005)
ADO (Kim et al. 2008b)
AFG3L2 (Li et al. 2005; Seitz et al. 2011)
AGMAT (Seitz et al. 2011)
AGPAT5 (Morrish et al. 2008; Seitz et al. 2011)
AIFM1 (Li et al. 2003, 2005)
AK2 (O'Connell et al. 2003; Li et al. 2005; Zeller et al. 2006; Kim et al. 2008a; Seitz et al. 2011)
AK3 (Zeller et al. 2006; Seitz et al. 2011)
AK4 (Seitz et al. 2011)
AKAP1 (Schuhmacher et al. 2001; Li et al. 2005; Seitz et al. 2011)
AKAP10 (Li et al. 2003; Seitz et al. 2011)
ALDH1B1 (Li et al. 2005; Seitz et al. 2011)
ALDH18A1 (Li et al. 2005; Seitz et al. 2011)
ALDH2 (Fernandez et al. 2003)
ALDH5A1 (Li et al. 2005; Seitz et al. 2011)
AMACR (Kim et al. 2008a)
AP2M1 (Kim et al. 2008a)
APEX1 (Ji et al. 2011)
ARG2 (Kim et al. 2008a)
ATAD3A (Morrish et al. 2008)
ATAD3B (Ji et al. 2011)
ATP5B (Li et al. 2003; Kim et al. 2008a; Seitz et al. 2011)
ATP5C1 (Fernandez et al. 2003; Li et al. 2003)
ATP5D (Zeller et al. 2006; Seitz et al. 2011)
ATP5E (Seitz et al. 2011)
ATP5G1 (Li et al. 2005; Seitz et al. 2011)
ATP5G2 (Li et al. 2003; Seitz et al. 2011)
ATP5G3 (Kim et al. 2008a)
ATP5I (Seitz et al. 2011)
ATP5J (Ji et al. 2011; Seitz et al. 2011)
ATP5L (Seitz et al. 2011)
ATP5S (Mao et al. 2003; Seitz et al. 2011)
ATPAF1 (Li et al. 2005)
ATPAF2 (Seitz et al. 2011)
ATPIF1 (Guo et al. 2000)
AUH (Schuhmacher et al. 2001)
BAX (Fernandez et al. 2003; Seitz et al. 2011)
BBC3 (Fernandez et al. 2003; Seitz et al. 2011)
BCAT2 (Seitz et al. 2011)
BCKDHA (Li et al. 2003; Kim et al. 2008a)
BCKDHB (Li et al. 2003, 2005)
BCL2 (Fernandez et al. 2003; Zeller et al. 2006; Seitz et al. 2011)
BCL2A1 (Zeller et al. 2006)
BCL2L1 (Seitz et al. 2011)
BCL2L11 (Seitz et al. 2011)
BCS1L (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
BDH1 (Li et al. 2005; Seitz et al. 2011)
BNIP3 (Zeller et al. 2006)
BNIP3L (Zeller et al. 2006)
C1QBP (Menssen and Hermeking 2002; Li et al. 2005; Seitz et al. 2011)
C10orf2 (Ji et al. 2011)
C12orf10 (Ji et al. 2011; Seitz et al. 2011)
C14orf159 (Zeller et al. 2006; Seitz et al. 2011)
C14orf2 (Li et al. 2005; Seitz et al. 2011)
C15orf62 (Seitz et al. 2011)
C17orf76-AS1 (Seitz et al. 2011)
C2orf47 (Seitz et al. 2011)
C21orf33 (Seitz et al. 2011)
Corf32 (Seitz et al. 2011)
CARS2 (Ji et al. 2011)
CASP8 (Seitz et al. 2011)
CCDC90A (Seitz et al. 2011)
CCDC90B (Seitz et al. 2011)
CHCHD2 (Ji et al. 2011; Seitz et al. 2011)
CHCHD3 (Seitz et al. 2011)
CHCHD4 (Seitz et al. 2011)
CISD1 (Kim et al. 2008a; Seitz et al. 2011)
CKMT2 (Fernandez et al. 2003)
CLIC4 (Shiio et al. 2006)
CLN3 (Seitz et al. 2011)
CLPP (Li et al. 2005; Seitz et al. 2011)
CLPX (Seitz et al. 2011)

Continued

Table 1. *Continued*

CLYBL (Seitz et al. 2011)
CMC1 (Seitz et al. 2011)
CMC2 (Li et al. 2005)
COA4 (Ji et al. 2011)
COQ2 (Seitz et al. 2011)
COQ3 (Li et al. 2005)
COQ4 (Ji et al. 2011; Seitz et al. 2011)
COQ9 (Seitz et al. 2011)
COQ10A (Seitz et al. 2011)
COX10 (Kim et al. 2008a)
COX11 (Li et al. 2005; Kim et al. 2008a)
COX15 (Li et al. 2003; Seitz et al. 2011)
COX16 (Li et al. 2005)
COX18 (Seitz et al. 2011)
COX4I2 (Zeller et al. 2006)
COX5A (Seitz et al. 2011)
COX5B (Fernandez et al. 2003; Morrish et al. 2003; Kim et al. 2008a)
COX6A1 (Morrish et al. 2003)
COX6A2 (Fernandez et al. 2003)
COX7A2L (Morrish et al. 2008)
COX7B (Kim et al. 2008a; Ji et al. 2011)
CPOX (Morrish et al. 2008)
CPT1A (Seitz et al. 2011)
CRAT (Mao et al. 2003; Seitz et al. 2011)
CRLS1 (Seitz et al. 2011)
CS (Kim et al. 2008a; Seitz et al. 2011)
CYB5-M (Kim et al. 2008a)
CYC1 (Seitz et al. 2011)
CYCS (Guo et al. 2000; Schuhmacher et al. 2001; Li et al. 2005; Morrish et al. 2008; Seitz et al. 2011)
CYP27B1 (Ji et al. 2011)
D2HGDH (Seitz et al. 2011)
DAP3 (Li et al. 2003)
DARS2 (Zeller et al. 2006)
DBI (Fernandez et al. 2003; Li et al. 2005)
DDX28 (Ji et al. 2011)
DEGS1 (Kim et al. 2008a)
DGUOK (Seitz et al. 2011)
DHODH (Schuhmacher et al. 2001; Li et al. 2005; Seitz et al. 2011)
DHX30 (Zeller et al. 2006; Seitz et al. 2011)
DIABLO (Li et al. 2003)
DLAT (Li et al. 2005; Seitz et al. 2011)
DLD (Seitz et al. 2011)
DLST (Seitz et al. 2011)
DNA2 (Li et al. 2005; Seitz et al. 2011)
DNAJA3 (Kim et al. 2008a; Ji et al. 2011; Seitz et al. 2011)
DNAJC11 (Seitz et al. 2011)
DNAJC19 (Zeller et al. 2006)
DUT (Li et al. 2005)
EARS2 (Seitz et al. 2011)
ECI1 (Li et al. 2005; Seitz et al. 2011)
ECSIT (Morrish et al. 2008; Seitz et al. 2011)
ELK3 (Seitz et al. 2011)
ENDOG (Li et al. 2005; Seitz et al. 2011)
ENOSF1 (Ji et al. 2011)
ESR2 (Seitz et al. 2011)
ETFDH (Jensen et al. 2011)
ETHE1 (Seitz et al. 2011)
FAM136A (Seitz et al. 2011)
FAM162A (Ji et al. 2011)
FANCG (Seitz et al. 2011)
FARS2 (Morrish et al. 2008)
FASTKD2 (Ji et al. 2011)
FDX1L (Seitz et al. 2011)
FECH (Fernandez et al. 2003)
FEN1 (Li et al. 2005; Seitz et al. 2011)
FH (Li et al. 2005; Seitz et al. 2011)
FIBP (Morrish et al. 2008; Seitz et al. 2011)
FPGS (Fernandez et al. 2003; Seitz et al. 2011)
FTSJ2 (Li et al. 2005)
FXC1 (O'Connell et al. 2003; Kim et al. 2008a)
FXN (Schuhmacher et al. 2001; Fernandez et al. 2003; Li et al. 2005; Seitz et al. 2011)
GARS (Seitz et al. 2011)
GBAS (Seitz et al. 2011)
GCAT (Li et al. 2005; Seitz et al. 2011)
GCDH (Morrish et al. 2008; Seitz et al. 2011)
GCET2 (Seitz et al. 2011)
GCSH (Schuhmacher et al. 2001; Li et al. 2005; Zeller et al. 2006)
GDAP1 (Li et al. 2003)
GFER (Morrish et al. 2008)
GFM1 (Li et al. 2005; Seitz et al. 2011)
GK (Morrish et al. 2008)
GLDC (Li et al. 2005; Zeller et al. 2006)
GLRX2 (Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)
GLS (Li et al. 2005)
GLS2 (Morrish et al. 2008)
GLUD1 (Zeller et al. 2006)
GLUD2 (Li et al. 2005)
GLYCTK (Seitz et al. 2011)
GOLPH3 (Mao et al. 2003)
GOT2 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
GPAM (Morrish et al. 2008)
GPAT2 (Fernandez et al. 2003)
GRPEL1 (Coller et al. 2000; O'Connell et al. 2003; Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)

Continued

Table 1. *Continued*

GRPEL2 (Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)
GSR (Kim et al. 2008a; Seitz et al. 2011)
GSTP1 (Fernandez et al. 2003)
GSTZ1 (Kim et al. 2008a)
GTPBP3 (Morrish et al. 2008; Seitz et al. 2011)
GTPBP5 (Seitz et al. 2011)
GUF1 (Zeller et al. 2006)
HADH (Fernandez et al. 2003; Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
HAGS (Seitz et al. 2011)
HARS2 (Seitz et al. 2011)
HAX1 (Li et al. 2003; Kim et al. 2008a)
HCCS (Li et al. 2003; Kim et al. 2008a)
HCLS1 (Seitz et al. 2011)
HIBADH (Seitz et al. 2011)
HIRIP5 (Morrish et al. 2008)
HK2 (Seitz et al. 2011)
HKDC1 (Seitz et al. 2011)
HLCS (Seitz et al. 2011)
HSCB (Seitz et al. 2011)
HSD17B8 (Seitz et al. 2011)
HSPA9 (Li et al. 2005; Seitz et al. 2011)
HSPD1 (Coller et al. 2000; Menssen and Hermeking 2002; Fernandez et al. 2003; O'Connell et al. 2003; Li et al. 2005)
HSPE1 (Schuhmacher et al. 2001; Menssen and Hermeking 2002; O'Connell et al. 2003; Li et al. 2005; Seitz et al. 2011)
HTRA2 (Seitz et al. 2011)
IARS2 (Seitz et al. 2011)
IBA57 (Seitz et al. 2011)
IDH2 (O'Connell et al. 2003)
IDH3A (Morrish et al. 2008)
IDH3B (Li et al. 2003, 2005; Zeller et al. 2006; Seitz et al. 2011)
IDH3G (Kim et al. 2008a; Seitz et al. 2011)
ILF3 (Seitz et al. 2011)
IMMPL2L (Zeller et al. 2006; Seitz et al. 2011)
IMMT (Kim et al. 2008a; Seitz et al. 2011)
ISCA1 (Seitz et al. 2011)
ISCU (Seitz et al. 2011)
ISOC2 (Seitz et al. 2011)
KARS (Kim et al. 2008a; Seitz et al. 2011)
KIAA1967 (Seitz et al. 2011)
KMO (Seitz et al. 2011)
L2HGDH (Zeller et al. 2006)
LARS2 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
LETM1 (Morrish et al. 2008; Seitz et al. 2011)
LIAS (Li et al. 2005)
LIPT1 (Li et al. 2003; Seitz et al. 2011)
LRPPRC (Morrish et al. 2008; Seitz et al. 2011)
LYRM2 (Kim et al. 2008a)
LYRM4 (Seitz et al. 2011)
MCAT (Morrish et al. 2008; Seitz et al. 2011)
MCCC1 (Seitz et al. 2011)
MCCC2 (Li et al. 2005; Seitz et al. 2011)
MCL1 (Fernandez et al. 2003)
MDH2 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
ME2 (Kim et al. 2008a; Ji et al. 2011; Seitz et al. 2011)
MECR (Morrish et al. 2008; Seitz et al. 2011)
METAP1D (Ji et al. 2011)
MFF (Seitz et al. 2011)
MFN2 (Morrish et al. 2008; Seitz et al. 2011)
MGST1 (Menssen and Hermeking 2002; Fernandez et al. 2003; Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
MIPEP (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
MLXIP (Seitz et al. 2011)
MMAA (Seitz et al. 2011)
MMAB (Li et al. 2005; Seitz et al. 2011)
MPC1 (Seitz et al. 2011)
MPC2 (Seitz et al. 2011)
MPV17 (Seitz et al. 2011)
MRM1 (Seitz et al. 2011)
MRPL1 (Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)
MRPL11 (Li et al. 2005)
MRPL12 (Li et al. 2005; Seitz et al. 2011)
MRPL13 (Li et al. 2005; Seitz et al. 2011)
MRPL14 (Seitz et al. 2011)
MRPL15 (Seitz et al. 2011)
MRPL16 (Morrish et al. 2008; Seitz et al. 2011)
MRPL17 (Seitz et al. 2011)
MRPL18 (Kim et al. 2008a)
MRPL19 (Li et al. 2005)
MRPL21 (Seitz et al. 2011)
MRPL (Morrish et al. 2008; Seitz et al. 2011)
MRPL23 (Fernandez et al. 2003; Li et al. 2005)
MRPL24 (Ji et al. 2011; Seitz et al. 2011)
MRPL27 (Zeller et al. 2006; Kim et al. 2008a; Seitz et al. 2011)
MRPL3 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
MRPL32 (Li et al. 2005; Zeller et al. 2006; Kim et al. 2008a)
MRPL34 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
MRPL36 (Li et al. 2005; Seitz et al. 2011)
MRPL37 (Li et al. 2005; Zeller et al. 2006)

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Table 1. *Continued*

MRPL38 (O'Connell et al. 2003; Seitz et al. 2011)
MRPL39 (Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)
MRPL4 (Seitz et al. 2011)
MRPL40 (Li et al. 2003; Kim et al. 2008a; Seitz et al. 2011)
MRPL42 (Li et al. 2005; Seitz et al. 2011)
MRPL43 (Kim et al. 2008a; Seitz et al. 2011)
MRPL44 (Seitz et al. 2011)
MRPL45 (Li et al. 2005)
MRPL46 (Zeller et al. 2006; Kim et al. 2008a; Seitz et al. 2011)
MRPL47 (Li et al. 2005)
MRPL48 (Zeller et al. 2006; Kim et al. 2008a; Seitz et al. 2011)
MRPL49 (Kim et al. 2008a)
MRPL50 (Li et al. 2005; Seitz et al. 2011)
MRPL51 (Kim et al. 2008a)
MRPL53 (Seitz et al. 2011)
MRPL54 (Seitz et al. 2011)
MRPL55 (Seitz et al. 2011)
MRPL9 (Morrish et al. 2008)
MRPS10 (Kim et al. 2008a)
MRPS12 (Li et al. 2005)
MRPS14 (Kim et al. 2008a; Seitz et al. 2011)
MRPS15 (Li et al. 2005; Seitz et al. 2011)
MRPS16 (Kim et al. 2008a; Seitz et al. 2011)
MRPS17 (Li et al. 2005)
MRPS18B (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
MRPS18C (Kim et al. 2008a)
MRPS2 (Li et al. 2005; Kim et al. 2008a)
MRPS21 (Kim et al. 2008a; Seitz et al. 2011)
MRPS22 (Li et al. 2005)
MRPS23 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
MRPS25 (Li et al. 2005; Seitz et al. 2011)
MRPS26 (Li et al. 2005; Seitz et al. 2011)
MRPS27 (Li et al. 2005; Zeller et al. 2006)
MRPS28 (Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)
MRPS30 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
MRPS31 (Seitz et al. 2011)
MRPS33 (Seitz et al. 2011)
MRPS34 (Li et al. 2005; Seitz et al. 2011)
MRPS35 (Li et al. 2005; Seitz et al. 2011)
MRPS36 (Kim et al. 2008a)
MRPS5 (Seitz et al. 2011)
MRPS7 (Zeller et al. 2006; Seitz et al. 2011)
MRRF (Ji et al. 2011; Seitz et al. 2011)
MRS2 (Seitz et al. 2011)
MSTO1 (Zeller et al. 2006; Seitz et al. 2011)
MTCH1 (Seitz et al. 2011)
MTCH2 (Seitz et al. 2011)
MTERF (Mao et al. 2003)
MTERFD1 (Seitz et al. 2011)
MTFMT (Li et al. 2005; Seitz et al. 2011)
MTFP1 (Ji et al. 2011)
MTFR1 (O'Connell et al. 2003; Seitz et al. 2011)
MTG1 (Seitz et al. 2011)
MTHFD1L (Zeller et al. 2006; Seitz et al. 2011)
MTHFD2 (Li et al. 2005; Seitz et al. 2011)
MTIF2 (Li et al. 2005; Seitz et al. 2011)
MTIF3 (Seitz et al. 2011)
MTO1 (Morrish et al. 2008; Seitz et al. 2011)
MTPAP (Ji et al. 2011)
MTRF1 (Seitz et al. 2011)
MTRF1L (Kim et al. 2008a)
MTUS1 (Kim et al. 2008b)
MTX2 (Zeller et al. 2006; Seitz et al. 2011)
MUT (Seitz et al. 2011)
MYCBP (Li et al. 2005)
MYL10 (Seitz et al. 2011)
NADKD1 (Seitz et al. 2011)
NARS2 (Zeller et al. 2006; Seitz et al. 2011)
NDUFA1 (Li et al. 2003, 2005; Kim et al. 2008a)
NDUFA11 (Ji et al. 2011)
NDUFA12 (Ji et al. 2011; Seitz et al. 2011)
NDUFA2 (Li et al. 2005)
NDUFA3 (Kim et al. 2008a)
NDUFA4 (Kim et al. 2008a)
NDUFA6 (Li et al. 2003; Kim et al. 2008a; Seitz et al. 2011)
NDUFA7 (Seitz et al. 2011)
NDUFA8 (Li et al. 2005)
NDUFAB1 (Li et al. 2005; Seitz et al. 2011)
NDUFAF2 (Tsuneoka et al. 2005; Ji et al. 2011)
NDUFAF3 (Morrish et al. 2008)
NDUFAF4 (Seitz et al. 2011)
NDUFAF6 (Seitz et al. 2011)
NDUFAF7 (Seitz et al. 2011)
NDUFB10 (Ji et al. 2011; Seitz et al. 2011)
NDUFB2 (Li et al. 2003; Kim et al. 2008a)
NDUFB3 (Li et al. 2005)
NDUFB5 (Li et al. 2005)
NDUFB6 (Zeller et al. 2006; Seitz et al. 2011)
NDUFB7 (Li et al. 2005; Kim et al. 2008a)
NDUFB9 (Kim et al. 2008a)
NDUFC1 (Kim et al. 2008a)
NDUFC2 (Seitz et al. 2011)

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Table 1. *Continued*

NDUFS1 (Li et al. 2003, 2005; Kim et al. 2008a; Seitz et al. 2011)
NDUFS5 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
NDUFS6 (Li et al. 2005)
NDUFS7 (Li et al. 2005; Seitz et al. 2011)
NDUFV1 (Li et al. 2003, 2005; Kim et al. 2008a; Seitz et al. 2011)
NDUFV2 (Seitz et al. 2011)
NDUFV3 (Seitz et al. 2011)
NEK9 (Seitz et al. 2011)
NELFE (Seitz et al. 2011)
NFS1 (Kim et al. 2008a)
NIPSNAP1 (Seitz et al. 2011)
NLN (Li et al. 2005; Seitz et al. 2011)
NME4 (Zeller et al. 2006)
NNT (Morrish et al. 2008)
NT5M (Seitz et al. 2011)
NUDT1 (Li et al. 2005)
NUDT19 (Seitz et al. 2011)
NUDT8 (Seitz et al. 2011)
OAT (Li et al. 2005)
OGDH (Seitz et al. 2011)
OGDHL (Li et al. 2005)
OGG1 (Seitz et al. 2011)
OPA1 (Kim et al. 2008a)
OPA3 (Kim et al. 2008a; Seitz et al. 2011)
OXCT1 (Li et al. 2005)
OXNAD1 (Jensen et al. 2011)
P4HA1 (Seitz et al. 2011)
PAM16 (Li et al. 2005)
PARK7 (Seitz et al. 2011)
PARL (Zeller et al. 2006)
PARS2 (Seitz et al. 2011)
PCCB (Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)
PCK2 (Morrish et al. 2008; Seitz et al. 2011)
PDF (Ji et al. 2011)
PDHA1 (Fernandez et al. 2003; Li et al. 2005)
PDHB (Fernandez et al. 2003; Seitz et al. 2011)
PDK1 (Li et al. 2003)
PDK2 (Li et al. 2003)
PDK3 (Li et al. 2003)
PDK4 (Kim et al. 2008a)
PDP1 (Seitz et al. 2011)
PDP2 (Seitz et al. 2011)
PEMT (Ji et al. 2011; Seitz et al. 2011)
PET112 (Li et al. 2003, 2005)
PGS1 (Seitz et al. 2011)
PHB (Menssen and Hermeking 2002; Fernandez et al. 2003; O'Connell et al. 2003; Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
PHB2 (O'Connell et al. 2003; Seitz et al. 2011)
PICK1 (Seitz et al. 2011)
PINK1 (Kim et al. 2008a; Seitz et al. 2011)
PITRM1 (Seitz et al. 2011)
PLD6 (Zeller et al. 2006)
PMAIP1 (Ji et al. 2011)
PMPCA (Li et al. 2003, 2005; Kim et al. 2008a)
PNPLA7 (Seitz et al. 2011)
PNPT1 (Ji et al. 2011; Seitz et al. 2011)
POLG (Kim et al. 2008a; Seitz et al. 2011)
POLG2 (Kim et al. 2008a; Seitz et al. 2011)
POLRMT (Li et al 2005)
PPA2 (Seitz et al. 2011)
PPIF (Coller et al. 2000; Menssen and Hermeking 2002; Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
PPOX (Seitz et al. 2011)
PPP1CC (Seitz et al. 2011)
PPP2CA (Li et al. 2003; Kim et al. 2008a)
PPP2R1A (Seitz et al. 2011)
PRDX3 (Wonsey et al. 2002; Li et al. 2005; Seitz et al. 2011)
PRDX5 (Li et al. 2003; Seitz et al. 2011)
PTCD2 (Zeller et al. 2006; Seitz et al. 2011)
PTCD3 (Ji et al. 2011)
PTPMT1 (Seitz et al. 2011)
PTRH2 (Kim et al. 2008a; Ji et al. 2011)
PUS1 (Li et al. 2005)
PYCR1 (Li et al. 2003; Seitz et al. 2011)
QARS (Seitz et al. 2011)
QTRTD1 (Ji et al. 2011; Seitz et al. 2011)
RAB1B (Morrish et al. 2008)
RAF1 (Seitz et al. 2011)
RARS2 (Seitz et al. 2011)
RBFA (Seitz et al. 2011)
RDH13 (Zeller et al. 2006)
REXO2 (Li et al. 2005; Seitz et al. 2011)
RHOT2 (Seitz et al. 2011)
RIPK1 (Seitz et al. 2011)
RMDN3 (Seitz et al. 2011)
RMRP (Fernandez et al. 2003)
RNASEH1 (Li et al. 2005)
RNF5 (Ji et al. 2011)
ROMO1 (Kim et al. 2008a; Seitz et al. 2011)
RPS6KB1 (Li et al. 2003)
RSAD1 (Seitz et al. 2011)
RSAD2 (Louro et al. 2002)
SAMM50 (Kim et al. 2008a)
SARDH (Guo et al. 2000; Seitz et al. 2011)
SARM (Seitz et al. 2011)
SARS2 (Kim et al. 2008a)
SCO1 (Li et al. 2005)

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Table 1. *Continued*

SCO2 (Zeller et al. 2006; Kim et al. 2008a; Seitz et al. 2011)
SDHA (Zeller et al. 2006; Kim et al. 2008a)
SDHAF1 (Seitz et al. 2011)
SDHB (Li et al. 2005; Seitz et al. 2011)
SDHD (Ji et al. 2011)
SEPW1 (Kim et al. 2008a)
SFXN1 (O'Connell et al. 2003; Li et al. 2005; Seitz et al. 2011)
SFXN3 (Mao et al. 2003)
SFXN3 (Seitz et al. 2011)
SFXN4 (Zeller et al. 2006; Seitz et al. 2011)
SHMT2 (Louro et al. 2002; Li et al. 2005; Seitz et al. 2011)
SIRT3 (Morrish et al. 2008)
SIRT5 (Seitz et al. 2011)
SLC22A4 (Seitz et al. 2011)
SLC25A1 (Seitz et al. 2011)
SLC25A10 (Fernandez et al. 2003; Seitz et al. 2011)
SLC25A11 (Li et al. 2003)
SLC25A12 (Seitz et al. 2011)
SLC25A13 (Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)
SLC25A15 (Seitz et al. 2011)
SLC25A17 (Li et al. 2005; Seitz et al. 2011)
SLC25A19 (Li et al. 2005; Seitz et al. 2011)
SLC25A20 (Seitz et al. 2011)
SLC25A22 (Morrish et al. 2008; Seitz et al. 2011)
SLC25A23 (Seitz et al. 2011)
SLC25A26 (Morrish et al. 2008)
SLC25A28 (Mao et al. 2003; Seitz et al. 2011)
SLC25A3 (Mao et al. 2003; Seitz et al. 2011)
SLC25A32 (Li et al. 2005; Kim et al. 2008a)
SLC25A33 (Seitz et al. 2011)
SLC25A36 (Seitz et al. 2011)
SLC25A37 (Morrish et al. 2008; Seitz et al. 2011)
SLC25A38 (Seitz et al. 2011)
SLC25A39 (Seitz et al. 2011)
SLC25A4 (Guo et al. 2000; Li et al. 2005)
SLC25A40 (Li et al. 2005; Seitz et al. 2011)
SLC25A42 (Seitz et al. 2011)
SLC25A45 (Seitz et al. 2011)
SLC25A5 (Morrish et al. 2008)
SLC25A51 (Kim et al. 2008a; Seitz et al. 2011)
SLC9B2 (Seitz et al. 2011)
SLIRP (Ji et al. 2011)
SMCR7L (Zeller et al. 2006; Seitz et al. 2011)
SOD2 (Li et al. 2005; Seitz et al. 2011)
SORD (Schuhmacher et al. 2001; Zeller et al. 2006)
SPG7 (Seitz et al. 2011)
SPNS1 (Seitz et al. 2011)
SSBP1 (Kim et al. 2008a; Ji et al. 2011; Seitz et al. 2011)
STARD7 (Seitz et al. 2011)
STOML2 (Morrish et al. 2008; Seitz et al. 2011)
SUCLG1 (Ji et al. 2011)
SUCLG2 (Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)
SUPV3L1 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
TACO1 (Ji et al. 2011; Seitz et al. 2011)
TARS2 (Seitz et al. 2011)
TFAM (Li et al. 2005; Seitz et al. 2011)
TFB1M (Morrish et al. 2008; Seitz et al. 2011)
TFB2M (Morrish et al. 2008; Seitz et al. 2011)
THG1L (Seitz et al. 2011)
TIMM10 (Li et al. 2005)
TIMM13 (Li et al. 2005; Seitz et al. 2011)
TIMM16 (Seitz et al. 2011)
TIMM17A (Li et al. 2005; Seitz et al. 2011)
TIMM17B (Kim et al. 2008a)
TIMM21 (Ji et al. 2011)
TIMM22 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
TIMM23 (O'Connell et al. 2003; Li et al. 2005)
TIMM44 (Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
TIMM50 (Seitz et al. 2011)
TIMM8A (Fernandez et al. 2003; Li et al. 2005; Kim et al. 2008a; Seitz et al. 2011)
TIMM8B (Li et al. 2003, 2005; Kim et al. 2008a; Seitz et al. 2011)
TIMM9 (Ji et al. 2011)
TIMMDC1 (Li et al. 2003; Kim et al. 2008a)
TK2 (Morrish et al. 2008; Seitz et al. 2011)
TMEM14C (Seitz et al. 2011)
TMEM126A (Seitz et al. 2011)
TMEM70 (Kim et al. 2008a; Seitz et al. 2011)
TOMM20 (Fernandez et al. 2003; Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)
TOMMS22 (Seitz et al. 2011)
TOMM23 (Li et al. 2005)
TOMM34 (Li et al. 2005; Seitz et al. 2011)
TOMM40 (Li et al. 2005; Seitz et al. 2011)
TOMM40L (Seitz et al. 2011)
TOMM5 (Seitz et al. 2011)
TOMM6 (Seitz et al. 2011)
TOMM7 (Li et al. 2005; Seitz et al. 2011)
TOMM70A (Li et al. 2005; Zeller et al. 2006; Kim et al. 2008a)
TOP1MT (Li et al. 2005)
TRAK1 (Seitz et al. 2011)

Continued

Table 1. *Continued*

TRAP1 (Coller et al. 2000; Schuhmacher et al. 2001; Menssen and Hermeking 2002; Li et al. 2005; Seitz et al. 2011)
TRIAP1 (Seitz et al. 2011)
TRIM39 (Ji et al. 2011)
TRIT1 (Li et al. 2005; Seitz et al. 2011)
TRMT10C (Seitz et al. 2011)
TRMU (Morrish et al. 2008; Seitz et al. 2011)
TRNT1 (Zeller et al. 2006; Seitz et al. 2011)
TSFM (Li et al. 2005; Seitz et al. 2011)
TSPO (Guo et al. 2000; Menssen and Hermeking 2002)
TUFM (Li et al. 2005; Seitz et al. 2011)
TXN2 (Seitz et al. 2011)
TXNRD2 (Seitz et al. 2011)
UCP1 (Fernandez et al. 2003; Li et al. 2005)
UCP2 (Fernandez et al. 2003; Zeller et al. 2006; Seitz et al. 2011)
UCP3 (Fernandez et al. 2003; Li et al. 2005)
UNG (Li et al. 2005; Seitz et al. 2011)
UQCRB (Li et al. 2005; Kim et al. 2008a)
UQCRC1 (Fernandez et al. 2003; Li et al. 2005)
UQCRC2 (Li et al. 2003, 2005; Kim et al. 2008a; Seitz et al. 2011)
URI1 (Ji et al. 2011)
UROS (Seitz et al. 2011)
USMG5 (Ji et al. 2011)
VAMP1 (Li et al. 2005; Kim et al. 2008a)
VARS2 (Li et al. 2003; Seitz et al. 2011)
VDAC1 (Guo et al. 2000; Li et al. 2005; Zeller et al. 2006; Seitz et al. 2011)
VDAC2 (Li et al. 2003; Seitz et al. 2011)
VDAC3 (Li et al. 2003, 2005)
WARS2 (Li et al. 2005; Zeller et al. 2006; Kim et al. 2008a; Seitz et al. 2011)
WWOX (Seitz et al. 2011)
XPNPEP3 (Zeller et al. 2006)
YARS2 (Li et al. 2005; Seitz et al. 2011)
YRDC (Seitz et al. 2011)
YWHAE (Seitz et al. 2011)
ZKSCAN1 (Seitz et al. 2011)

Unlike MYC, ERR-α, -β, -γ, PGC-1-α, -β, NRF-1, and GABP are highly expressed in tissues with increased metabolic activity (heart, kidney, liver, intestine, skeletal muscle, brown adipose tissue) and respond to metabolic cues at the organismal level (fasting, exercise, cold) (Giguere 2008). ERR-α/γ, PGC-1-α, and PPAR-α are also involved in a substrate switch from glucose to fatty acid oxidation via up-regulation of PDK4, a kinase that inactivates the pyruvate dehydrogenase complex (Wende et al. 2005). Notably, PGC-1β, NRF-1, GABPA, GABPB2, PPAR-α, PRC, and ERR-α have been reported as downstream targets of MYC (Li et al. 2003; O'Connell et al. 2003; Zeller et al. 2006; Zhang et al. 2007; Kim et al. 2008a,b; Morrish et al. 2008). It is worth noting that MYC has also been proposed to act as a transcriptional amplifier for all active genes (Lin et al. 2012; Nie et al. 2012).

MYC REGULATION OF MITOCHONDRIAL MASS

An effect of MYC on mitochondrial activity was initially noted in studies of the action of MYC on cell growth independent of cell division (Schuhmacher et al. 1999). P493-6 B cells expressing a conditional MYC allele increase in size, without entering S phase. An indicator of mitochondrial reducing activity, 3-(4,5-dimethylthiazol-2-yl)-2 2,5-diphenyl tetrazolium bromide (MTT), increased with MYC expression in nondividing cells.

MYC expression was definitively linked to mitochondrial biogenesis using nonyl acridine orange (NAO), a fluorescent probe that binds to the mitochondria-specific lipid cardiolipin, independent of mitochondrial function (Li et al. 2005). Although a slight increase in mitochondrial mass was observed in the P493-6 B-lymphocyte cell line upon MYC induction in the absence of serum, a more robust response was obtained with cells proliferating in serum-containing media. The overall function of cellular mitochondria, assessed by a membrane potential–sensitive dye, Mitotracker Red, and cellular oxygen consumption, increased in both conditions. Similar studies in fibroblasts have shown that maximal increases in mitochondrial mass and membrane potential induced by ectopic MYC expression may take 3–4 wk (Graves et al. 2012).

To determine if MYC was also required for normal mitochondrial biogenesis, Rat1 fibroblasts with targeted disruptions of both *MYC*

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gene copies were compared with $MYC^{+/+}$ cells and *MYC*-null cells expressing ectopic *MYC* (Li et al. 2005). NAO staining showed a pronounced loss of mitochondrial mass in the majority of *MYC*-null cells (with a smaller population of cells with near-normal mitochondrial content), and partial restoration of mitochondrial mass in MYC-rescued cells. Finally, acute deletion of floxed *MYC* from primary mouse hepatocytes by adenoviral infection with Cre recombinase produced diminished NAO and Mitotracker Red signals within 2 d. Differences in mitochondrial interconnectivity and subcellular location have also been observed, with MYC-rescued cells showing a perinuclear mitochondrial network, whereas *MYC*-null cells have single mitochondria dispersed throughout the cytoplasm (Graves et al. 2012). MYC-expressing cells have higher rates of mitochondrial fusion in PEG-fusion assays of cells containing different mitochondria-localized fluorophores.

MYC STIMULATES MITOCHONDRIAL BIOGENESIS AND METABOLISM DURING CELL-CYCLE ENTRY

The best-studied context for metabolic regulation by MYC is during cell-cycle entry. Initiation of cell cycling requires high metabolic activity for biosynthesis, and mitochondrial content, respiration, and membrane potential all increase during cell-cycle entry. A threefold to fourfold increase in oxygen consumption is observed in fibroblasts, whereas *MYC*-null fibroblasts show minimal changes (Morrish et al. 2008). Mitochondrial membrane potential and reactive oxygen species (ROS) are also increased in serum-stimulated fibroblasts compared with $MYC^{-/-}$ cells. (In contrast, during exponential growth, *MYC*-null fibroblasts generate higher levels of ROS than $MYC^{+/+}$ cells.) Fibroblasts expressing MYC are selectively sensitive to growth inhibition by mitochondrial poisons compared with *MYC*-null cells, consistent with a greater reliance on oxidative phosphorylation (OxPhos) for MYC-dependent cell-cycle entry. Cell proliferation at 48 h after serum stimulation is highly correlated with oxygen consumption for MYC-expressing cells treated with OxPhos inhibitors. $MYC^{-/-}$ cell proliferation tracks poorly with oxygen consumption.

ATP levels in MYC-positive cells are supported by OxPhos to a greater extent than in MYC-negative cells (Morrish et al. 2008; Bellance et al. 2012; Murphy et al. 2013). However, the effects of metabolic inhibitors on cell proliferation cannot be explained solely by changes in ATP. For example, cell proliferation in MYC-positive cells is unaffected by 2-deoxyglucose (2-DG), a glycolytic inhibitor, despite a twofold reduction in ATP concentration (Morrish et al. 2008). $MYC^{-/-}$ cells are less sensitive to growth inhibition with OxPhos inhibitors than with 2-DG, despite similar reductions in ATP levels. These observations suggest that mitochondrial metabolic processes other than bioenergetics support growth in MYC-expressing cells. In particular, MYC-positive cells appear to be more efficient at converting glucose into biomass. Treatment of $MYC^{+/+}$ cells with OxPhos inhibitors produces a phenocopy of $MYC^{-/-}$ cell-cycle entry in the absence of inhibitors.

Stable isotope tracer measurements using ^{13}C-labeled glucose, glutamine, or acetate show changes in mitochondrial metabolism during cell-cycle entry that correlate with mitochondrial biogenesis due to endogenous MYC induction (Morrish et al. 2010; Dang 2013). MYC-expressing cells use pyruvate dehydrogenase to complete glucose oxidation, compared with the predominantly anaplerotic entry of pyruvate through pyruvate carboxylase in $MYC^{-/-}$ cells. MYC also promotes utilization of TCA cycle intermediates for biosynthesis, including fatty acids from acetyl-CoA generated by glucose oxidation or glutamine metabolism, and NADPH from malic enzyme, as well as posttranslational histone acetylation (Wise et al. 2008; Morrish et al. 2010; Murphy et al. 2013). MYC appears unique in its ability to increase substrate availability for enzymes that are targets of its transcriptional activity.

SPECIAL CONSIDERATIONS WITH MYC OVEREXPRESSION

MYC overexpression has similar, but exaggerated, effects on mitochondrial biogenesis, oxida-

tive metabolism of nonglucose substrates, and sensitivity to OxPhos inhibitors (Fan et al. 2010; Murphy et al. 2013). One notable difference is in the oxidative metabolism of glucose in mitochondria. Induction of endogenous MYC during cell-cycle entry is associated with a twofold increase in glucose oxidation, whereas inducible overexpression of MYC has been reported to inhibit glucose oxidation (Wise et al. 2008; Morrish et al. 2009; Fan et al. 2010; but see Murphy et al. 2013). This may reflect suppression of mitochondrial glucose metabolism under conditions of high glucose availability, akin to the Crabtree effect (Redman et al. 2013), or low pyruvate availability due to substrate channeling.

In addition to basal respiration, MYC overexpression increases both spare and total reserve respiratory capacity (Bellance et al. 2012; Graves et al. 2012). Blue native gel electrophoresis analysis of mitochondrial complexes showed decreased content of OxPhos complexes in $MYC^{-/-}$ cells compared with $MYC^{+/+}$ cells, as well as reduced supercomplexes containing complexes I, III, and IV, and dimeric complex V.

The effects of MYC on mitochondrial biogenesis can be neutralized by coexpression of HIF proteins. HIFs are positive regulators of Mxi1, a MYC-related transcription factor that competes for binding to Max. Under extreme hypoxic conditions, HIFs promote ubiquitin-dependent proteolysis of MYC (Zhang et al. 2007). HIF-1 also induces FoxO3A, which antagonizes MYC activity at mitochondrial gene promoters (Jensen et al. 2011).

Supraphysiological levels of MYC can be associated with mitochondrial dysfunction, possibly due to imbalanced production of mitochondrial protein complex subunits or mitochondrial protein import in excess of mitochondrial protein folding and assembly capacity (Morrish et al. 2003). Mice with induced MYC expression in cardiomyocytes develop a fatal hypertrophic cardiomyopathy, with increased mitochondrial number and density, but decreased mitochondrial size (Lee et al. 2009). Citrate synthase, complex I, and complex III activities, as well as mitochondrial reserve, were reduced in mitochondria from MYC-overexpressing hearts, associated with reduced content of cytochromes *b*, *c*, and aa_3. Rescue of *MYC*-null cells with ectopic MYC only partially restores the content of OxPhos complexes and supercomplexes present in $MYC^{+/+}$ cells, possibly because of metabolic adaptations associated with deregulated MYC (Graves et al. 2012).

Overexpression of MYC can create an ATP deficit that requires activation of the AMP-dependent protein kinase and its upstream activator, AMP-related kinase 5 (ARK5) (Liu et al. 2012). ARK5 depletion results in lower oxygen consumption rates and reduced entry of α-ketoglutarate into the tricarboxylic acid (TCA) cycle, as well as reduced flow into citrate, in ^{13}C flux experiments. In these studies, ARK5 is required for posttranscriptional, nonproteasomal regulation of protein expression for several OxPhos subunits of complexes I, III, and IV in MYC-transformed cells. The inability to oxidize NADH may explain the observed TCA cycle defects.

Relative impairment of mitochondrial function with MYC overexpression may contribute to the Warburg effect (aerobic glycolysis) in cancer, as well as the phenomenon of MYC-dependent apoptosis.

CONCLUDING REMARKS

Despite the clear evidence that MYC stimulates mitochondrial biogenesis, the biological significance of this regulation is less well understood compared with several other transcription factors and coactivators whose mitochondrial roles have been well studied (see above). One fairly obvious difference is that MYC is a proto-oncogene and the other factors are not. In its oncogenic role, MYC is expressed at supraphysiological levels and reprograms metabolic flux patterns as part of the cancer phenotype (Hanahan and Weinberg 2011). Direct comparison of central carbon metabolism with high or low MYC expression showed that increased TCA cycle and amphibolic fluxes are the major differences observed with high-level MYC expression (Murphy et al. 2013).

MYC is a key, obligate driver of cell-cycle entry and progression, and one of its many functions in this context is to promote mito-

chondrial biogenesis in preparation for cell division, and oxidative metabolism as a source of energy and chemical intermediates for biosynthesis.

Studies in *Drosophila* have implicated MYC in a nutrient-sensing response (Teleman et al. 2008). TOR, involved in cellular sensing of amino acid availability and energy status, and FOXO, a transcription factor negatively regulated by the insulin/PI3K (phosphatidylinositol-3-kinase)/Akt signaling pathway, regulate MYC levels in response to nutrient deprivation. TOR induces MYC primarily at a posttranscriptional level, whereas FOXO has tissue-specific effects as a transcriptional regulator of MYC. These results suggest that MYC is an essential link between nutrient availability and macromolecular synthesis. Mitochondrial biogenesis, in addition to increasing bioenergetic capacity, supports lipid, protein, carbohydrate, and heme biosynthesis by transforming glucose and glutamine into key building blocks (see Dang 2013). In this context, MYC could function as a flexible adaptor, converting available nutrients into anabolic growth (Fig. 2).

MYC is also induced in response to the uncoupling agent, CCCP (Gleyzer and Scarpulla 2011), suggesting that MYC may have functions in mitochondrial responses to stress. An illustrative example is the myocardial response to pressure overload or ischemia (Ahuja et al. 2010). Adult cardiomyocytes principally rely on fatty acid oxidation (FAO) but undergo a stress-induced shift to glucose oxidation characteristic of fetal cardiomyocytes. This metabolic plasticity is associated with mitochondrial biogenesis, which is dependent on rapid MYC up-regulation. Myc also directs the substrate shift by transactivating multiple glycolytic enzymes and down-regulating FAO genes by inhibiting PGC-1α expression. The negative regulation of PGC-1α by MYC occurs at a posttranscriptional level, but the mechanism is unknown.

This example suggests that MYC regulation of mitochondrial biogenesis may also affect the choice of mitochondrial fuel. The switch from FAO to glucose oxidation has beneficial effects on myocardial performance and survival. Several other examples of fuel choice affecting cel-

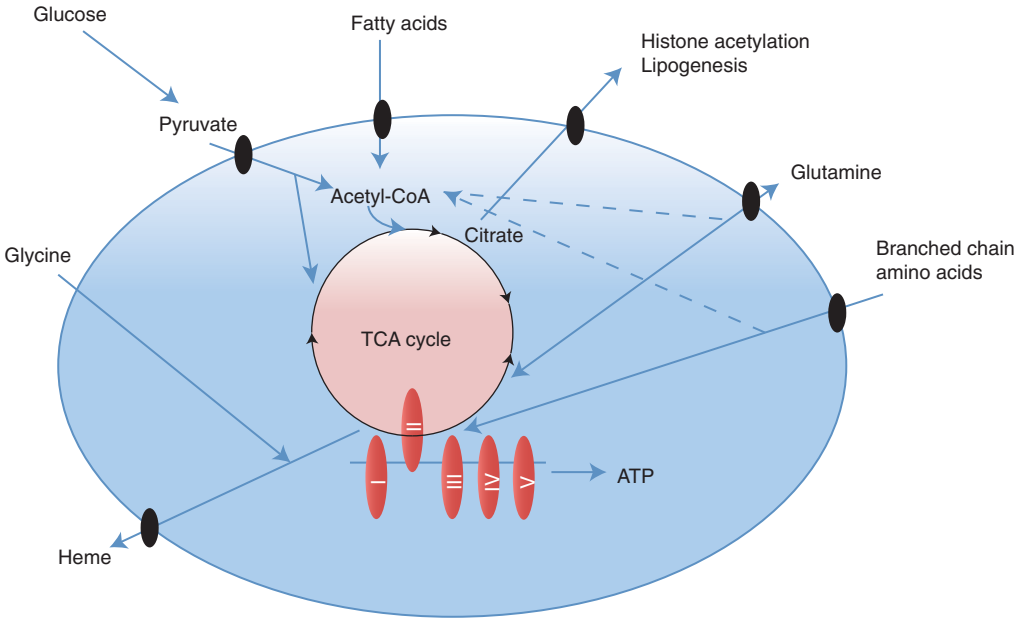

Figure 2. MYC-dependent mitochondrial biogenesis provides building blocks for anabolic synthesis in addition to ATP. Anabolic and catabolic pathways (arrows) regulated by MYC convert available nutrients to building blocks.

lular phenotype have recently been reported (Folmes et al. 2011; Ito et al. 2012; Van der Windt et al. 2012; Knobloch et al. 2013). The next phase of investigations of the role of MYC in mitochondrial biogenesis will likely include tissue-specific contexts of hyperplastic or hypertrophic responses to stress, fuel choice, and control of cellular phenotype, in order to complete this story.

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