**MYC oncogene promotes tissue-specific dedifferentiation gene expression changes in tumorigenesis**

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**Summary**

MYC is a transcription factor frequently overexpressed in cancer. To determine how MYC drives the neoplastic phenotype, we performed transcriptomic analysis using a panel of MYC-driven autochthonous transgenic mouse models. We found that MYC elicited gene expression changes in a tissue-specific manner across B-cell lymphoma, T-cell acute lymphoblastic lymphoma, hepatocellular carcinoma, renal cell carcinoma, and lung adenocarcinoma. However, despite these gene expression changes being highly tissue-specific, we uncovered convergence on a common pattern of upregulation of embryonic stem cell gene programs and downregulation of tissue-of-origin gene programs across MYC-driven cancers. These changes, representative of tissue dedifferentiation, may be facilitated by epigenetic alterations that occur during tumorigenesis. Moreover, we discovered that while several cellular processes are represented among embryonic stem cell genes, ribosome biogenesis is most specifically associated with MYC expression in human primary cancers whereas other pathways, such as DNA replication, have weaker correlation with MYC and therefore, although being important in tumorigenesis, may not necessarily be specific to MYC-driven cancers. Altogether, MYC’s capability to drive tumorigenesis in diverse tissue types appears to be related to its ability to promote tissue dedifferentiation.

**Introduction**

The MYC proto-oncogene, when mutated or overexpressed, has been implicated in the pathogenesis of most types of human cancer (Dang, 2012). MYC activation, in tandem with other genetic and epigenetic insults, results in initiation of tumorigenesis (Gabay et al., 2014). Cancers driven by MYC become dependent on its sustained oncogenic activity, a phenomenon known as oncogene addiction (Felsher, 2010; Li et al., 2014; Weinstein, 2002). Hence, despite the genomic complexity of cancers, inactivation of MYC alone can cause reversal of the neoplastic phenotype (Felsher and Bishop, 1999; Jain et al., 2002; Shachaf et al., 2004).

MYC orchestrates a transcriptional program of genes involved in proliferation, survival, self-renewal, ribosome biogenesis, mitochondrial biogenesis, glucose and glutamine metabolism, nucleotide biosynthesis, lipogenesis, angiogenesis, and immune evasion (Baudino et al., 2002; Dang, 2013; Felsher, 2010; Gouw et al., 2019; Li et al., 2014). Genes regulated by MYC in cancer could present druggable targets. Thus, uncovering bona fide MYC-regulated genes could have promising therapeutic implications for MYC-driven cancers (Chen et al., 2018).

MYC acts as a transcriptional amplifier that can also specifically induce or suppress gene expression (Lin et al., 2012; Muhar et al., 2018; Nie et al., 2012; Sabò et al., 2014; Walz et al., 2014). Moreover, MYC and its proximal network are generally involved in human cancer (Schaub et al., 2018). Clearly, MYC regulates the expression of many genes and many reports have identified MYC gene signatures (Bild et al., 2006; Ciribilli and Borlak, 2017; Ji et al., 2011; Jung et al., 2017; Wu et al., 2008; Zeller et al., 2003). However, it is less clear if MYC regulates any common set of genes required for tumorigenesis. Alternatively, MYC may upregulate genes in a particular cancer that are needed for the growth and survival of a particular cellular lineage. MYC’s transcriptional network has been suggested to be cell type and context dependent (Dang et al., 2006). Therefore, the gene expression changes elicited by MYC that are generally important for tumorigenesis versus for pathogenesis of a specific cancer still remain elusive.

Many studies have used experimental cancer models or human clinical specimens to identify genes regulated by MYC. A recent study identified a prognostic MYC gene signature through microarray analysis of a transgenic murine model of MYC-induced lung adenocarcinoma (Ciribilli and Borlak, 2017). Other studies have probed the transcriptional landscape of MYC using human clinical specimens. One such study derived a prognostic MYC gene signature in human epithelial ovarian cancer and neuroblastoma (Jung et al., 2017). Furthermore, a pan-cancer analysis of The Cancer Genome Atlas (TCGA) data identified multi-cancer MYC-associated pathways (Schaub et al., 2018).

Here, we examined how MYC regulates gene expression across different types of cancers using five genetically engineered mouse models (GEMMs) including tetracycline (Tet)-regulated conditional transgenic mouse models (Yeh et al., 2014) of MYC-induced renal cell carcinoma (RCC) (Shroff et al., 2015), hepatocellular carcinoma (HCC) (Shachaf et al., 2004), lung adenocarcinoma (LAC) (Tran et al., 2008), T-cell acute lymphoblastic lymphoma (T-ALL) (Felsher and Bishop, 1999), and a transgenic model of B-cell lymphoma (BCL) (Adams et al., 1985). In all these models, MYC can be overexpressed in a tissue-specific manner, allowing us to interrogate tissue-specific changes in gene expression brought about by MYC. Our findings point to large heterogeneity in gene expression changes among different MYC-driven cancer types. Despite this heterogeneity, we find that the gene expression changes across different MYC-driven cancers manifest a common profile of tissue dedifferentiation, represented by alterations in embryonic stem cell-like gene programs, particularly ribosome biogenesis genes, as well as tissue-of-origin gene programs.

**Results**

**Differentially Expressed Genes in MYC-Induced Cancer**

We used conditional transgenic mouse models with tissue-specific inducible MYC expression for RCC, HCC, LAC, and T-ALL (Felsher and Bishop, 1999; Shachaf et al., 2004; Shroff et al., 2015; Tran et al., 2008) (**Supplementary Fig. 1**) under the Tet System (Gossen and Bujard, 1992; Yeh et al., 2014). For BCL, we leveraged RNA-seq data from the transgenic model of Eμ‑Myc lymphomagenesis (Adams et al., 1985; Sabò et al., 2014).

We performed differential gene expression analysis on these five transgenic mouse tumor models (**Table 1**), comparing MYC-induced tumor tissue to control normal tissue (**Fig. 1a**). Genes were considered differentially expressed (DE) if they changed at least 2-fold with adjusted p-value < 0.05. This analysis unveiled thousands of DE genes (**Supplementary Table 1**), only 44 of which were common to all five transgenic mouse models (**Fig. 1b, Supplementary Fig. 2**). Thus, there is large heterogeneity in differentially expressed genes among the five MYC-driven transgenic mouse tumor models.

**Tissue Lineage Specificity of MYC Cancer Gene Signatures**

Tissue enrichment analysis was performed using differential gene expression data for each of the five transgenic mouse models to identify whether specific tissue-lineages were enriched among the differentially expressed genes. Tissue-lineage genes, which consist of genes abundantly expressed in a given tissue type, were derived from the BioGPS Mouse Gene Atlas (Su et al., 2004; Wu et al., 2009). We specifically investigated gene sets of liver, kidney, lung, and spleen tissue, which were the tissue-of-origin of the mouse tumors. Additionally, we explored embryonic stem cell genes, which are commonly overexpressed in cancer (Ben-Porath et al., 2008). We identified that, across MYC-driven cancers, the upregulated genes were enriched in embryonic stem cell (ESC) genes (**Fig. 1c**) while downregulated genes for a given cancer type were enriched in genes abundantly expressed in the respective tissue-of-origin (**Fig. 1d, Supplementary Table 2**). However, in KRAS-driven LAC, although lung tissue genes were downregulated, ESC genes were not upregulated unlike in MYC-driven cancers, demonstrating that different oncogenes alter different gene programs to promote tumorigenesis. Taken together, the results suggest that MYC-driven cancers repress corresponding tissue-lineage genes and promote ESC gene profiles.

We identified, using gene set enrichment analysis (GSEA), the top gene ontology (GO) terms associated with the differential gene expression profiles in each MYC-induced transgenic mouse tumor model (**Fig. 2, Supplementary Table 3**). Related GO terms were grouped into pathways (**Supplementary Table 4**). Across models, programs related to cell cycle control, DNA replication, chromatin organization, protein synthesis, RNA processing, and ribosome biogenesis were consistently upregulated by MYC activation. This is congruent with long-standing knowledge about MYC’s role in regulating cell proliferation (Dang, 2013) and with reports suggesting a cell-type independent function of MYC is to drive biomass accumulation (Ji et al., 2011). We also observed tissue-specific pathway enrichment patterns, such as downregulation of lipid metabolism genes in HCC and RCC, downregulation of ion transport genes in RCC, downregulation of immune response genes in T-ALL and BCL, and downregulation of angiogenesis genes and extracellular matrix (ECM) organization genes in LAC. However, we were careful to note that the corresponding tissue-of-origin also showed enrichment for these pathways (**Supplementary Table 5**). For example, genes abundantly expressed in normal kidney tissue exhibit enrichment for ion transport and genes abundantly expressed in normal lung tissue exhibit enrichment for angiogenesis. Furthermore, embryonic stem cell genes showed enrichment for the MYC-upregulated pathways. Thus, these pathway enrichment results for the differential gene expression profiles are likely just a consequence of the normal tissue gene expression profile becoming dedifferentiated, lending further support for the importance of considering dedifferentiation in interpreting gene expression changes in MYC-driven cancers.

**Epigenetic Changes Underlying MYC-Driven Differential Gene Expression in Cancer**

To investigate the mechanisms underlying the gene expression changes in MYC-induced tumorigenesis, we explored chromatin immunoprecipitation sequencing (ChIP-seq) data from the HCC and BCL transgenic mouse models (Kress et al., 2016; Sabò et al., 2014). Comparing tumor to normal tissue, promoters of upregulated genes in each model became enriched in H3K4me3 and H3K27ac, histone marks of active transcription, while promoters of downregulated genes became depleted of these marks (**Fig. 3a**). Next, we looked at superenhancers (Khan and Zhang, 2016) associated with the differentially expressed genes (**Supplementary Table 6**). We found tissue-specific changes in superenhancer activity in that, for each tumor model, most superenhancers associated with the upregulated genes became enriched in H3K27ac, an active enhancer mark, while most superenhancers associated with the downregulated genes became depleted in H3K27ac (**Fig. 3b, Supplementary Fig. 3**). Of note, liver tissue superenhancers tended to be associated with the downregulated genes, not the upregulated genes, in HCC and the same was observed for spleen tissue superenhancers with regards to BCL. This agrees with our gene expression analyses showing the high tissue-of-origin specificity of downregulated genes. These results collectively show that MYC‑driven tumors have an altered epigenetic state that is consistent with gene expression changes.

**Identification of a Gene Signature Associated with MYC Expression in Human Cancers**

Human TCGA pan-cancer RNA-seq data of 9354 patient primary cancer samples across 33 cancer types were used to identify genes associated with MYC expression. We performed pairwise Pearson correlation between each gene and MYC gene expression values and performed robust rank aggregation (RRA) (Kolde et al., 2012) using the Pearson correlation coefficients (Pearson’s r) for each gene across the 33 cancer types (**Fig. 4a, Supplementary Table 7**). We considered genes with median Pearson’s r > 0.30 and RRA adjusted p‑value < 0.05 to be MYC-correlated genes. These genes are the ones most likely to be specific to MYC’s activity whereas genes with lesser correlation may be involved in many cancers in general, not just those with high MYC expression. We considered tumorigenesis-associated genes to be those upregulated in at least 4 out of 5 MYC-driven mouse tumor models. These genes are likely to be important in MYC-induced tumorigenesis as they have been demonstrated upregulation across multiple MYC-driven mouse tumor models. These genes are also generally upregulated in TCGA human cancers (**Supplementary Fig. 4**). We filtered the 251 tumorigenesis-associated genes that had a human ortholog to only include genes that are also MYC-correlated, resulting in a final set of 67 genes (**Fig. 4b, Supplementary Table 8**). These 67 genes, unlike the other 184 tumorigenesis-associated genes that aren’t as strongly correlated with MYC expression, are enriched in ribosome biogenesis and RNA metabolism genes but do not exhibit enrichment for DNA replication, cell division, and chromatin organization pathways which were highly enriched among the other 184 genes (**Fig. 4c, Supplementary Table 9**). Both the 67-gene signature and the remaining 184 tumorigenesis-associated genes are enriched in embryonic stem cell genes. Together, these results suggest that while embryonic stem cell genes are involved in multiple pathways and are upregulated in MYC-driven cancers, some pathways like ribosome biogenesis tend to be more specific for MYC activity.

The 67-gene signature forms a densely interconnected protein-protein interaction network (**Fig. 4d**), representative of the fact that most of the genes are related in function. We further validated five signature genes: UCK2, YBX3, NOP56, NOB1, and MARS2 plus the MYC-downregulated gene, SLC46A3, by RT‑qPCR in two cell lines which possess tetracycline-regulated MYC overexpression: P493-6 cells, a transformed human B cell line, and EC4 cells, a tumor-derived mouse HCC cell line. RT‑qPCR confirmed MYC inactivation (**Supplementary Fig. 5**) and confirmed that all these genes, barring SLC46A3, were significantly downregulated by MYC inactivation, while SLC46A3 either showed no change or slight upregulation (**Fig. 4e**).

We additionally validated the 67-gene signature using cancer cell line RNA-seq data from the Cancer Cell Line Encyclopedia (CCLE) (Ghandi et al., 2019) and human cancer survival data from TCGA. Using t-SNE clustering on CCLE expression data of our 67-gene signature separated cancer cells with high MYC expression from those with low MYC expression fairly well (**Fig. 5a**). Several signature genes such as NOB1, RSL1D1, and MARS2 were among the genes most correlated with MYC expression (Pearson’s r > 0.475) across the CCLE cancer cell lines (**Supplementary Table 11**). To assess prognostic value, we calculated meta-analysis z scores (meta-z scores) quantifying prognostic significance of genes across the 33 TCGA cancer types in a similar manner to previously published methods (Gentles et al., 2015). The 67 signature genes generally have positive meta-z scores, suggesting poor prognosis in cancer (**Fig. 5b, Supplementary Table 10**). Ribosome biogenesis is a known MYC pathway (Barna et al., 2008; van Riggelen et al., 2010) and many genes in this signature have been implicated in MYC-driven cancer including: PRMT5 (Koh et al., 2015), NOP56 (NOL5A) (Cowling et al., 2014), IMPDH2 (Liu et al., 2008; Mannava et al., 2008), UCK2 (Ciribilli et al., 2016), and GNL3 (Zwolinska et al., 2012), among others. However, other genes have not been implicated in MYC pathways: METTL13, NOA1, MARS2, etc. We investigated multiple previously published MYC gene sets (**Supplementary Table 12**) (Alfano et al., 2010; Bild et al., 2006; Coller et al., 2000; Ellwood-Yen et al., 2003; Ji et al., 2011; Jung et al., 2017; Menssen and Hermeking, 2002; Muhar et al., 2018; Schaefer et al., 2009; Schuhmacher et al., 2001; Yu et al., 2005; Zeller et al., 2003) and observed that they were quite dissimilar from one another and featured only a small amount of overlap with these 67 genes (**Fig. 5c**). Of note, 19 genes in the 67-gene signature were not present in the 16 previously published MYC gene sets we investigated as part of this study. However, our signature performs comparably to, if not better than, most previously published sets of MYC-upregulated genes in terms of correlation with MYC expression across CCLE cell lines (**Fig. 5d**) and in terms of prognostic value (**Fig. 5e**). In summary, our 43-gene signature contains both previously identified and novel MYC-associated genes.

**Discussion**

MYC and its associated network of interacting gene products are important to the regulation of gene transcription and have been implicated in the pathogenesis of most types of human cancer (Schaub et al., 2018). Here we have performed a multi-cancer transcriptomic analysis on transgenic mouse models to reveal that although the genes differentially expressed in MYC-driven tumorigenesis depend on the tissue in which MYC is overexpressed, a common gene expression pattern of tissue dedifferentiation emerges across different types of MYC-driven tumors.

Our results are the first to look across multiple MYC-driven conditional transgenic mouse models. We identified MYC-driven differential gene expression profiles in BCL (3843 DE genes), T-ALL (6803 DE genes), HCC (2435 DE genes), RCC (2344 DE genes) and LAC (1339 DE genes) using transgenic mouse models. We noted a very limited degree of overlap in DE genes among the different models, suggesting that the DE genes are highly tissue-specific. This could be one reason why, while many previous reports have defined MYC gene signatures (Bild et al., 2006; Ciribilli and Borlak, 2017; Ji et al., 2011; Jung et al., 2017; Wu et al., 2008; Zeller et al., 2003), often the gene lists are dissimilar. Moreover, our work agrees that while MYC may function as a general amplifier of gene expression (Lin et al., 2012; Nie et al., 2012), it also selectively affects particular sets of genes (Muhar et al., 2018; Sabò et al., 2014; Walz et al., 2014).

We had wondered whether the disparate differential gene expression profiles represented different pathways or different genes within the same pathway. We hypothesized that because MYC overexpression can drive tumorigenesis in various tissue types, the disparate differential gene expression profiles should converge on a common oncogenic theme. Indeed, we found that MYC appears to commonly upregulate embryonic stem cell-like gene programs and downregulate tissue-of-origin gene programs in tumorigenesis, alterations that are representative of tissue dedifferentiation. Our results have implications for how MYC initiates and maintains a cancer state.

We therefore propose a model whereby MYC overexpression causes a new tissue state to form which allows for tissue-specific dedifferentiation gene expression changes (**Fig. 6**). These changes depend on what the initial tissue type is. For example, the downregulated genes for a given cancer type tend to be enriched in genes that are highly expressed in the tissue type from which the cancer originated and not other tissue types. We suggest that the gene expression profile formed in the new tumor tissue state is likely the result of both direct effects of MYC on gene expression in its capacity as a transcription factor as well as epigenetic changes. These epigenetic changes, specifically in enhancer and promoter activity markers, that occur in MYC-driven tumorigenesis are corroborated by our analysis of ChIP-seq data. MYC is known to epigenetically alter gene expression by directly recruiting proteins that catalyze histone modifications (Frank et al., 2001; Martinato et al., 2008) and by reprogramming cell state (Farrell et al., 2017; Takahashi and Yamanaka, 2006). In breast cancer, it has been shown that MYC-driven epigenetic reprogramming represses luminal lineage-specifying transcription factors and induces a stem cell-like state (Poli et al., 2018). Our results implicate that MYC may function in a similar way across multiple other tissue types.

Genes that more broadly seem to be regulated by MYC across cancers appear to mostly be related to embryonic stem cell genes. The upregulation of embryonic stem cell genes in cancer has been suggested previously (Ben-Porath et al., 2008; Wong et al., 2008) and stem cell pluripotency, like MYC-driven cancers, depends on higher rates of rRNA synthesis and ribosome biogenesis (Brombin et al., 2015; Turi et al., 2019; Watanabe-Susaki et al., 2014). We realized that even genes broadly differentially expressed across MYC-driven cancers in transgenic mouse models may not necessarily be specific to MYC-driven cancers. To identify genes that are more likely to be specific to MYC-driven cancers, we explored the TCGA dataset and narrowed our MYC gene signature to a set of 67 genes that were at least moderately correlated with MYC expression in primary human cancers. These 67 genes, unlike the genes with weaker correlation with MYC, were significantly enriched in ribosome biogenesis genes suggesting that ribosome biogenesis is most specific to MYC-driven cancers. In contrast, other pathways, such as DNA replication and cell division, might not depend specifically on MYC activity but rather are features of many cancers in general. As our 67 MYC gene signature is prognostic in human cancers, can separate MYC-high from MYC-low cancers, and many of these genes have not been reported in previously published MYC gene sets, these genes warrant further investigation as potential vulnerabilities in MYC-driven cancers.

Altogether, our findings suggest that the transition to the tumor tissue state involves specific epigenetic and transcriptional profile changes, which are dictated by both MYC overexpression and the initial tissue state. Since tumorigenesis is a multi-step process (Land et al., 1983), it is probable that a step-wise succession of feedback loops involving gene expression changes gives rise to new cellular states. As such, future work should explore the progression of the dedifferentiation gene expression trajectory over a tumorigenesis time course. Finally, future studies, should explores the effect of other members of the MYC proximal network that shield a more nuanced insight into how gene expression is regulated in a specific manner across cancer types (Schaub et al., 2018).

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**Author contributions**

D.K.S. – Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Visualization, Project administration

A.D. – Formal analysis, Writing – review and editing

R.D. – Formal analysis, Writing – review and editing

M.S.K. – Validation

A.M.G. – Formal analysis

D.I.B. – Resources

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D.F.L. – Data Curation, Writing – review and editing

D.W.F. – Conceptualization, Supervision, Project administration, Funding acquisition, Writing – review and editing

**Declaration of Interests**

The authors have no conflicts of interest to disclose.

**Methods**

**Code Availability**

For transparency of methods, all the code and procedures that can be used to reproduce the results in this paper, starting from the raw data, are available at https://github.com/Yenaled/felsher and the relevant data from all public datasets used in this study (e.g. TCGA, CCLE, dbSUPER, etc.) are also accessible via this repository.

**Mouse Microarray and RNA-Seq Data Analysis and Availability**

All mouse microarray and RNA-Seq data used in this study are publicly available on the Gene Expression Omnibus (GEO) repository. Microarrays were performed by the Stanford Functional Genomics Facility using Illumina mouse microarray platforms. The microarray data is available at GEO accession number GSE143254. The microarray data was further processed to remove poorly detected probes (detection p-value > 0.01 across all samples) followed by quantile-normalization then log2-transformation using the R package, lumi (version 2.38.0). All animal studies, which were performed to generate the microarray datasets, were approved by the Stanford University Administrative Panel on Laboratory Animal Care (APLAC). Eμ‑Myc RNA-seq data (Sabò et al., 2014) and T-ALL RNA-seq data (Swaminathan et al., 2020) from previous studies were obtained from GEO (accession numbers GSE51008 and GSE106078, respectively). For RNA-seq, kallisto (version 0.44.0) (Bray et al., 2016) was used to pseudoalign raw reads to the GRCm38 (mm10) mouse with 100 bootstraps. The R libraries, limma (version 3.42.0) (Smyth, 2004) and sleuth (version 0.30.0) (Pimentel et al., 2017), were used for differential gene expression analysis of microarray and RNA-seq data, respectively.

**Analysis of TCGA and CCLE RNA-Seq Data**

Human RNA-seq data from The Cancer Genome Atlas (TCGA) was downloaded from the UCSC Xena Toil project (Vivian et al., 2017), which provides the log2-transformed RSEM expected counts (Li and Dewey, 2011) normalized using DESeq2 (Love et al., 2014). The R library, ComBat (Johnson et al., 2007), was used for batch effect correction in TCGA data using biospecimen batch identifier data obtained from the National Cancer Institute's Genomic Data Commons (GDC) data portal. RNA-seq TPM data from the Cancer Cell Line Encyclopedia (CCLE) was obtained from the Broad Institute and this data was further normalized using the DESeq2 method followed by log2-transformation.

**Gene List Analysis**

Enrichment analysis, providing odds ratios and Fisher’s exact test p-values to test the representation of gene sets given a list of genes, was performed using Enrichr (Kuleshov et al., 2016). For gene ontology (GO) terms, the Biological Process category is used (Ashburner et al., 2000). Gene set enrichment analysis (GSEA) (Subramanian et al., 2005) was performed on the log2 fold change differential gene expression profiles of each of the five transgenic mouse tumor models using the fgsea (version 1.12.0) R package (Korotkevich et al., 2019). Protein-protein interaction network analysis was performed using the STRING database (Szklarczyk et al., 2019), with the settings "meaning of network edges": "confidence", "active interaction sources": all selected, "minimum required interaction score": 0.400, and "max number of interactors to show": "query proteins only".

**ChIP-Seq Analysis**

MYC and histone ChIP-Seq data were processed using the ENCODE ChIP-Seq pipeline (Landt et al., 2012) (with Macs2 as the peak caller) and further analyzed using deepTools (Ramírez et al., 2016). For ChIP-Seq analysis of mouse superenhancer regions, mouse superenhancer genomic coordinates and associated gene symbols were obtained from dbSUPER (Khan and Zhang, 2016) and the coordinates were converted to mm10 coordinates using the UCSC Genome Browser tool: liftOver.

**Survival Analysis**

TCGA patient overall survival data was obtained from the TCGA Pan-Cancer Clinical Data Resource (TCGA-CDR) dataset (Liu et al., 2018). The z-scores from the Cox proportional hazards regression model for each gene were obtained using the coxph function of the survival (version 3.1-12) package in R and were aggregated across all TCGA cancer types into meta-z scores via Stouffer's method (unweighted) akin to the methods described in PRECOG (Gentles et al., 2015).

**Cell Culture**

P493-6 cells were maintained in RPMI 1640 medium (with L-glutamine) supplemented with 10% FBS and Antibiotic-Antimycotic. EC4 cells and HuH7 cells were maintained in maintained in Dulbecco's Modified Eagle Medium (DMEM) (with 4.5g/L D-glucose), supplemented with 10% fetal bovine serum (FBS), 1% L-glutamine, 1% sodium pyruvate, 1% nonessential amino acids, and Antibiotic-Antimycotic. For these cell lines, MYC inactivation was achieved by adding doxycycline to the culture medium at a concentration of 20 ng/mL. BJ5ta cells were maintained in media supplemented with 10% FBS that consisted of a 4:1 ratio of DMEM (with 4.5 g/L D-Glucose), supplemented with 1% L-glutamine and 1% sodium pyruvate, to Medium 199.

**Reverse Transcription Quantitative Polymerase Chain Reaction (RT-qPCR)**

RNA was isolated from cells by the RNeasy Mini Kit (QIAGEN) and reverse-transcribed into cDNA using the SuperScript III First-Strand Synthesis kit (ThermoFisher) following manufacturer's protocol. Quantitative PCR was performed in 384-well plates on the QuantStudio 12K Flex Real-Time PCR System, using SYBR Green I dye as fluorophore to detect amplicons. Reactions were carried out in 20-μL volumes that contained 0.5 μL cDNA, 0.25 μM forward and reverse primers, and SYBR Green PCR Master Mix (Applied Biosystems). The following amplification cycle settings were used: 50 °C for 2 minutes; 95 °C for 10 minutes; and 40 cycles of 95 °C for 15 seconds, 60 °C for 1 minute, and 72 °C for 30 seconds. The 2−∆∆CT method was used to plot relative mRNA levels with UBC serving as a reference gene. Primers used in this study are shown in **Supplementary Table 13**.

**False Discovery Rates**

All false discovery rate (FDR) adjusted p-values were determined by the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995).

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