Overexpression of the c-myc Oncogene Inhibits Nonsense-mediated RNA Decay in B Lymphocytes*

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Background: The Myc transcription factor plays an important role in physiology and cancer. The repression of NMD by Myc contributes to the Myc ability to regulate genes.

Results: High expression of Myc inhibits nonsense-mediated RNA decay (NMD), leading to the stabilization and up-regulation of mRNAs.

Conclusion: The repression of NMD by Myc contributes to the Myc ability to regulate genes.

Significance: This novel function of Myc may play an important role in Myc-dependent tumorigenesis.

The c-myc gene plays an important role in normal cellular growth, proliferation, and differentiation, and myc dysregulation plays a causal role in many human malignancies. The Myc transcription factor performs these cellular functions by regulating gene expression through a variety of mechanisms. For example, Myc transcriptionally up-regulates genes involved in cancer, including those involved in cell cycle activation, protein synthesis, and amino acid and carbohydrate metabolism (for review, see Refs. 1, 2). Myc has also been demonstrated to repress a select group of transcripts (3). However, in contrast to the well described role of Myc in gene transcription, the role of Myc in mRNA stability has not been extensively explored.

Nonsense-mediated RNA decay (NMD) is a well established mechanism to rapidly degrade mutated mRNAs responsible for many human genetic diseases (for review, see Ref. 4). NMD has also been implicated in tumorigenesis (for review, see Ref. 5). A systematic analysis of mutations in human genes has revealed that although most mutation in oncogenes are missense mutations, tumor suppressor genes exhibit a disproportionate number of NMD-provoking mutations (6), and although NMD has traditionally been thought of as a mechanism to protect an organism from deleterious dominant negative or gain-of-function effects of truncated proteins that arise from mutated transcripts, NMD has recently been found to regulate up to 10% of nonmutated transcripts, many of which play roles in tumorigenesis (7–9).

It has also been determined recently that NMD is a regulated process that can dynamically alter gene expression. NMD is inhibited by a variety of cellular stresses that commonly occur in the tumor microenvironment (7–9). This inhibition of NMD promotes tumorigenesis, likely in part by stabilizing several transcripts important for the cellular response to stress, including the transcription factor ATF-4 (7–9). Myc also promotes the metabolic adaptation to hypoxia and other stresses, in part by generating reactive oxygen species (ROS) which stabilizes the hypoxia-inducible transcription factor-1α (10–12) (for review, see Ref. 13). Because ROS generation leads to the phosphorylation of translation factor eIF2α (14) and we have recently demonstrated that the phosphorylation of eIF2α inhibits NMD (8–9), we hypothesized that oncogenic stress resulting from Myc dysregulation inhibits NMD. We therefore investigated whether Myc inhibits NMD, whether this occurs via phosphorylation of eIF2α, and the significance of NMD inhibition on the stabilization and up-regulation of Myc targets.

MATERIALS AND METHODS

Cell Lines and Treatments—P493-6 B (P493) cells were maintained in RPMI 1640 medium with 10% FBS and 1% penicillin-streptomycin. Burkitt lymphoma cell lines (GM04678, GM04679, GM08686, GM08687, GM08688, GM0689, and CRL01432) were obtained from the Coriell Institute for Medical Research, and the low Myc-expressing B lymphoma cell line diacetate; PERK, PKR-like ER kinase; CHOP, CCAAT/enhancer-binding protein-homologous protein.
FIGURE 1. Myc stabilized a NMD reporter. A, Myc expression in P493-6 cells, modulated as described under “Results,” was determined by immunoblotting. B, P493 cells expressing either wild-type or PTC 39 β-globin constructs were treated so they expressed high, low, or intermediate levels of Myc, and β-globin mRNA stability was assessed by treating cells with DRB and serially assessing globin RNA levels by RT-quantitative PCR at the indicated time points. β-Globin mRNA is normalized to expression of 18 S RNA. Three biological replicates were performed, and the average ± S.E. (error bars) is displayed. The left panel displays β-globin mRNA expression normalized to time 0 for each condition. The right panel displays β-globin mRNA expression as a ratio, with each condition normalized to low Myc expression at each time point; values >1 (dashed line) reflect stabilization.

RESULTS

Myc Inhibits NMD—To investigate the effect of Myc expression on NMD activity, we first utilized the P493 cell line which contains an inducible Myc expression system. In these cells tetracycline treatment tightly represses ectopic Myc protein expression and results in low endogenous Myc expression (Fig. 1A) (16). This cell line also expresses an Epstein-Barr virus EBNA2 gene as an estrogen-activated construct (ER-EBNA2), and in the presence of estradiol-forced cell proliferation leads to intermediate expression of Myc. As a first step to assess NMD activity, we engineered these cells to express either a wild-type β-globin gene or a mutated β-globin gene that carries a single nucleotide substitution that leads to a premature termination codon (β-globin PTC 39) and thus encodes a transcript that is degraded by NMD. NMD activity was then determined by inhibiting transcription with the RNA II polymerase inhibitor DRB and serially assessing globin transcript expression under conditions resulting in low Myc (tetracycline), high Myc (no tetracycline), and intermediate Myc levels (cells either grown without tetracycline for 8 h or grown in the presence of tetracycline and estradiol for 8 h) (Fig. 1A). Myc expression in P493 cells in the absence of tetracycline was equivalent to that seen in Burkitt lymphoma cell lines (data not shown).

The stability of wild-type β-globin mRNA was comparable under all three Myc expression levels (Fig. 1B). In contrast, the stability of the PTC 39 β-globin mRNA was dramatically increased in cells with high Myc expression and resembled that of the wild-type β-globin mRNA stability. Under the two conditions that led to moderate levels of Myc, the stability of the PTC 39 β-globin mRNA was slightly increased compared with cells with low Myc expression. When expressed as a ratio of stability in high Myc-expressing cells to stability in low Myc-expressing cells, the β-globin PTC 39 mRNA was ~4-fold stabilized (Fig. 1B, right). These data suggest that high Myc expression, as seen in many malignancies, can inhibit NMD.

Myc Inhibits NMD via Generation of ROS and Phosphorylation of eIF2α—Because we recently demonstrated that NMD is inhibited by phosphorylation of eIF2α, which occurs as a result of a variety of cellular stresses (9), we investigated the possibility that eIF2α phosphorylation is enhanced by high expression of Myc. eIF2α phosphorylation is mediated by a variety of kinases, including the endoplasmic reticulum (ER)-residing kinase PERK which is activated when unfolded proteins accumulate in the ER, a condition stimulated by the glycosylation inhibitor tunicamycin. Although there was only a minimal increase in
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Base-line elf2α phosphorylation in high Myc-expressing P493 cells, we noted a marked robust phosphorylation of elf2α with tunicamycin treatment in those cells with elevated Myc in contrast to cells with low Myc (Fig. 2A). elf2α phosphorylation promotes the translation of the stress response transcription factor ATF-4, and we observed a rapid induction of ATF-4 and its target CHOP when cells with elevated Myc were treated with tunicamycin compared with cells with low Myc expression treated with tunicamycin (Fig. 2B, top). Processing of the XBP-1 transcription factor by the ER-residing IRE1 endonuclease serves as a surrogate marker of ER stress, and splicing of XBP-1 also occurred dramatically in response to tunicamycin in cells expressing Myc highly, and much slower in cells with low Myc expression (Fig. 2B, bottom). Together, these data suggest that high Myc expression sensitizes cells to enhanced ER stress and phosphorylation of elf2α.

The generation of ROS leads to PERK-mediated phosphorylation of elf2α (14). We assessed whether the ability of Myc to generate ROS (10–11) plays an important role in its inhibition of NMD. As expected, cells expressing high levels of Myc exhibited a significant increase of ROS compared with cells expressing lower levels of Myc, and this effect decreased when cells were cultured with the ROS scavenger N-acetylcysteine (Fig. 2C).

Similarly, the concentration of intracellular H2O2 was increased with elevated Myc expression, as assessed by oxidation of 10-acetyl-3,7-dihydroxyphenoxazine (Amplex Red) (Fig. 2D). N-Acetylcysteine did not change the stability of the wild-type β-globin mRNA, but the PTC 39 β-globin mRNA was no longer stabilized in high Myc cells in the presence of N-acetylcysteine (Fig. 2E).

To determine whether elf2α phosphorylation is necessary for Myc inhibition of NMD (as it is for the inhibition of NMD in hypoxic or tunicamycin-treated cells) (8, 9), we expressed Myc or a control retrovirus in elf2α wild-type MEFs and in MEFs in which elf2α cannot be phosphorylated due to the presence of mutated elf2α alleles (elf2α S51A MEFs) (Fig. 2F). These cells also expressed either wild-type or the PTC 39 β-globin construct. In wild-type elf2α MEFs, Myc overexpression selectively stabilized the PTC 39 β-globin transcript ~2-fold compared with the control infected elf2α wild-type cells (Fig. 2G). In contrast, Myc overexpression did not significantly alter the stabilization of the β-globin PTC 39 transcript in the elf2α

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**FIGURE 2.** High Myc expression leads to ROS-mediated ER stress and inhibition of NMD. A, P493 cells with either high or low Myc expression were treated with tunicamycin (Tm) for the described time points, and phosphorylated elf2α induction was assessed by immunoblotting. Total elf2α was served as a control. Two biological replicates were performed, and average fold inductions ± S.E. (error bars) are noted graphically in the lower panel. B, ATF-4 and CHOP protein expression were assessed by immunoblotting in high Myc and low Myc-expressing P493 cells (top). Cells were also harvested for RNA, and RT-PCR was performed to determine the ratio of spliced to unspliced XBP-1 (bottom). C, P493 cells with high Myc expression, low Myc expression, or high Myc expression with and without 5 mM N-acetylcysteine were stained with H2-DCFDA, and fluorescence was assessed by FACS. D, P493 cells with low Myc or Myc induced with the withdrawal of tetracycline for 2 and 4 h were assessed for H2O2 species as described under “Materials and Methods.” Experiments were performed in triplicate, with average ± S.E. shown, *<0.05 versus low Myc. E, the stability of wild-type and PTC 39 β-globin mRNA was assessed in the cells described in C. NAC, N-acetylcysteine. F, elf2α wild-type and elf2α S51A cells (which do not phosphorylate elf2α in response to tunicamycin (Tm), top panel) were infected with control (MSCV) or Myc (MSCV-Myc) viruses (bottom panel). G, globin mRNA stability was assessed in cells described in F. Three biological replicates were performed, and average ± S.E. are displayed. H, PTC39 globin mRNA expression was assessed in PERK wild-type and PERK-deficient MEFs in the absence and presence of Myc.
S51A MEFs, indicating that eIF2α phosphorylation is required for the inhibition of NMD by Myc. When Myc was overexpressed in wild-type PERK MEFs, we again noted stabilization of the β-globin PTC 39 transcript (Fig. 2H). Such stabilization was not observed in PERK−/− MEFs. Together, these data indicate that high Myc expression can promote eIF2α phosphorylation and inhibit NMD through a ROS- and PERK-dependent mechanism.

Myc Stabilizes Endogenous NMD Transcripts—Although NMD was originally thought to be responsible for degrading only mutated transcripts, a number of studies have identified nonmutated transcripts also degraded by NMD (7–9). Because the NMD-targeted PTC39 β-globin transcript is stabilized by high Myc expression, we next investigated whether endogenous NMD-targeted transcripts, including transcripts vital for the cellular response to stress, are stabilized by Myc. We found that the transcripts for ATF-4 and several other NMD targets were significantly stabilized in high Myc-expressing P493 cells compared with low Myc-expressing cells (Fig. 3A), thus confirming that NMD is inhibited by Myc.

Of 2100 transcripts found to be up-regulated by Myc in human B (P493) cells (17) and 694 transcripts stabilized by the pharmacological, molecular, and environmental inhibition of NMD in human osteosarcoma (U2OS) cells (9), 63 genes were common to both sets. Of note, this number of NMD targets also up-regulated by Myc is likely a low estimate because the databases compared were derived from different cell lines and Myc targets are cell context-dependent (18). We arbitrarily chose eight of these transcripts and confirmed that all eight were stabilized with the addition of the translational inhibitor emetine (Fig. 3B and data not shown). Six of these transcripts also displayed increased stabilities in cells with either high or intermediate Myc expression compared with low Myc expression (Fig. 3B), indicating that elevated Myc expression can also suppress the NMD-mediated degradation of endogenous Myc targets.

The regulation of steady-state gene expression is a complex function of both synthesis and degradation, and we next explored whether the inhibition of NMD by Myc can contribute to the up-regulation of Myc targets. We assessed pre-mRNA (mRNAs containing introns) expression as an indicator of newly synthesized mRNA, and processed mRNA (mRNAs without introns) expression as an indicator of both transcription and post-transcriptional processes. When we examined four Myc targets that are not targeted by NMD, three genes displayed elevation of both pre-mRNAs and mRNAs to similar extents in response to high Myc expression, and none of the genes at the pre-mRNA or mRNA level was significantly

![Figure 3. Myc inhibition of NMD stabilizes and up-regulates NMD and Myc targets. A, the stability of NMD targets was assessed in low Myc- and high Myc-expressing P493 cells by inducing Myc, serially collecting RNA in the absence of transcription, and performing quantitative PCR for the indicated transcripts at 0, 1.5, 3, and 4.5 h. Results were normalized to 18S RNA expression. Results for each time are displayed as expression with high Myc/expression low Myc. B, six transcripts previously found to be up-regulated by Myc and stabilized by the inhibition of NMD were assessed for stability with low Myc, intermediate Myc, and high Myc levels as defined under “Materials and Methods.” Emetine-treated low and intermediate Myc-expressing cells are displayed as controls. n = 3 with *, p < 0.05 of high Myc versus low Myc for individual time points. C, the mRNA and pre-mRNA expression of transcripts previously determined to be up-regulated by Myc or both Myc and NMD were assessed in low Myc-expressing cells, high Myc-expressing cells, and low Myc-expressing cells that were treated with emetine. Average ± S.E. (error bars) of duplicate experiments are displayed.](image-url)
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affected by emetine (Fig. 3C). One Myc target, GPR54, was only minimally elevated at the pre-mRNA level despite a marked induction at the mRNA level. This transcript has not been identified as a NMD target and indeed was not induced by emetine, suggesting that another mechanism may play a role in its post-transcriptional up-regulation. In contrast, seven transcripts that have been reported to be up-regulated by both Myc and NMD demonstrated significant increases in steady-state mRNA expression with either high Myc expression or emetine treatment. As expected, emetine treatment alone did not increase transcription (i.e. increase the pre-mRNAs) of any of these genes. Although two of these transcripts (HSPA14, SNHG8) showed significant induction of pre-mRNA with high Myc expression, the rest showed minimal increases of pre-mRNA and/or mRNA induction out of proportion to pre-mRNA induction. Together, these data suggest that the inhibition of NMD by Myc plays a contributing role in the up-regulation of a set of Myc targets.

elf2α Is Phosphorylated and NMD Targets Stabilized in Cell Lines Derived from Burkitt Lymphoma—We next investigated whether NMD is also inhibited in cell lines derived from Burkitt lymphoma, a tumor marked by high Myc expression, compared with a variety of other B cell lymphoma cell lines with lower Myc expression (Fig. 4A and data not shown). Consistent with our model that the inhibition of NMD by Myc requires elf2α phosphorylation, we observed a high correlation of elf2α phosphorylation with Myc expression in these cell lines (Fig. 4A).

We then assessed the stability of several NMD targets in these cell lines. ATF-4 mRNA was significantly (p < 0.05) stabilized >2-fold in all Burkitt lymphoma cell lines compared with its stability in the low-Myc non-Burkitt cell lines (Fig. 4B). Similarly, the stabilities of five NMD-degraded mRNAs that were stabilized by Myc in P493 cells (Fig. 3B) were also significantly stabilized in the Burkitt lymphoma cell lines (Fig. 4C). In addition, published expression analyses of genes overexpressed in Burkitt lymphomas compared with reactive lymph nodes (19) showed a significant (p < 0.002) overlap with mRNAs we have reported previously to be targeted by NMD (Fig. 4D). Specifically, there was an almost 2-fold increase in NMD targets up-regulated in these cell lines compared with what would be expected randomly. Together, these data suggest that the inhibition of NMD noted with exogenous Myc overexpression may also be observed in human tumors with high Myc expression.

DISCUSSION

Myc is best known for affecting gene expression by directly transactivating and repressing genes. However, many genes up-regulated by Myc are not direct targets, i.e. have Myc bound at their promoters (18). In addition, a recent study noted that many of the transcripts up-regulated by Myc are not induced at the transcriptional level, suggesting that post-transcriptional processes may play an important role in their up-regulation (20). Consistent with these findings, Myc has recently been appreciated to regulate microRNAs that can then affect mRNA stability (21). Our data indicate that an additional mechanism by which Myc regulates gene expression is by inhibiting NMD and stabilizing a select set of transcripts. This not only represents an important new aspect of Myc biology, but also increases the significance of NMD regulation, particularly in tumorigenesis.

It has long been appreciated that the expression levels between individual Myc targets vary. Although the reasons for this observation are complex and include the presence of cooperating transcription factors and epigenetic modifications, our data suggest that the inhibition of NMD can play an important role in augmenting the expression of Myc targets that are also targeted by NMD. An analysis of mRNAs stabilized by the inhibition of NMD (9) found a significant (p < 0.5 × 10^-4) overlap...
with mRNAs bound by Myc (18), suggesting that even mRNAs transcriptionally activated by Myc may be stabilized by Myc inhibition of NMD for maximum induction (data not shown).

We found that although Myc stabilizes most of the NMD targets we examined, not all NMD targets are up-regulated in cells expressing high Myc. Indeed, many NMD targets (e.g. ATF-4) have not been defined as classic Myc targets, highlighting the complex regulation of Myc targets by several distinct and perhaps competing mechanisms. Consistent with this finding, we have found that many transcripts stabilized by NMD inhibition are not necessarily up-regulated with NMD inhibition (8, 9). For example, the ATF-4 transcript is a bona fide NMD target, but even when it is stabilized by the hypoxic inhibition of NMD its expression is unchanged from its expression in normoxic cells. However, emphasizing the importance of NMD inhibition are not necessarily up-regulated with NMD inhibition (8, 9). For example, the ATF-4 transcript is a NMD target, but even when it is stabilized by the hypoxic inhibition (8, 9). For example, the ATF-4 transcript is a NMD target, but even when it is stabilized by the hypoxic inhibition (8, 9). For example, the ATF-4 transcript is a NMD target, but even when it is stabilized by the hypoxic inhibition (8, 9).

The phosphorylation of eIF2α in response to cellular stress is a dynamic process and dependent on the coordinated actions of multiple eIF2α kinases and eIF2α phosphatases, some of which themselves activated by stress (for review, see Ref. 22). Although we did not note a dramatic base-line increase in basal, steady-state eIF2α phosphorylation with high expression of Myc in P493 cell, eIF2α phosphorylation correlated with Myc expression level in a variety of lymphoma cell lines. We also observed that high Myc expression renders cells more sensitive to ER stress and eIF2α phosphorylation in P493 cells. There are several potential mechanisms by which Myc could promote phosphorylation of eIF2α and thus inhibit NMD. First, Myc induces protein synthesis severalfold, which could lead to the accumulation of unfolded proteins in the ER, activation of PERK, and phosphorylation of eIF2α (23). Second, Myc promotes rapid proliferation which leads to replication stress and/or DNA damage that can promote eIF2α phosphorylation (for review, see Refs. 12, 24). Because of the Myc ability to generate ROS we favor a third possibility, that direct generation of ROS by Myc could either promote unfolded proteins in the ER and/or activate ROS-responsive eIF2α kinases (14). Because PERK appears necessary for Myc-induced phosphorylation of eIF2α, it is likely that unfolded ER proteins do accumulate with high Myc expression. ROS scavengers, such as N-acetylcysteine, could blunt several of these Myc phenotypes, and we are unable to distinguish between these possibilities at this time.

Although Myc is primarily known as a pro-proliferative oncogene, Myc also plays important roles in angiogenesis and tumor metabolism and enhances three-dimensional growth (for review, see Ref. 13). We have determined previously that the inhibition of NMD also stabilizes and up-regulates several stress response genes, improves cellular survival to ER stress, and augments three-dimensional tumor growth (8, 9). The inhibition of NMD is therefore an additional mechanism by which Myc may promote tumorigenesis. NMD also degrades many mutated tumor suppressor transcripts, including p53 and BRCA1 (for review, see Ref. 5), and the stabilization of these transcripts could lead to truncated proteins, some of which exhibit dominant negative properties. Thus, the role Myc inhibition of NMD plays in tumorigenesis is potentially extensive and deserves further study.

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