The c-myc gene encodes a sequence-specific DNA binding protein that activates transcription of cellular genes. Transcription activation by Myc proteins is regulated by phosphorylation of serine and threonine residues within the transactivation domain and by complex formation with the retinoblastoma-related protein p107. In Burkitt’s lymphoma, missense mutations within the c-Myc transactivation domain have been found with high frequency. It has been reported that mutant c-Myc proteins derived from Burkitt’s lymphoma cell lines are resistant to inhibition by p107, thus providing a rationale for the increased oncogenic activity of these mutant c-Myc proteins. It has been suggested that these mutant c-Myc proteins resist down-modulation by p107 because they lack cyclin A-cdk2-dependent phosphorylation. Here, we have examined three different Burkitt’s lymphoma mutant c-Myc proteins found in primary Burkitt’s lymphomas and one mutant c-Myc protein detected in a Burkitt’s lymphoma cell line. All four have an unaltered ability to activate transcription and are sensitive to inhibition of transactivation by p107. Furthermore, we provide evidence that down-modulation of c-Myc transactivation by p107 does not require phosphorylation of c-Myc transactivation domain by cyclin A-cdk2. Our data indicate that escape from p107-induced suppression is not a general consequence of all Burkitt’s lymphoma-associated c-Myc mutations, suggesting that other mechanisms exist to deregulate c-Myc function.

The proto-oncogene c-myc encodes a short-lived nuclear phosphoprotein with important roles in cellular proliferation, differentiation, neoplasia, and apoptotic cell death (for review, see Lüscher and Eisenman (1990) and Marcu et al. (1992)). A rapid increase in c-myc expression is observed when quiescent cells are stimulated to re-enter the cell cycle by growth factor stimulation (Kelly et al., 1983). In continuously proliferating cells, however, c-myc mRNA and protein levels are invariant throughout the cell cycle (Hann et al., 1985; Thompson et al., 1986). Insight into the function of Myc proteins came from the identification of two motifs in the carboxyl terminus of Myc proteins that are present in several transcription factors: the basic-helix-loop-helix (bHLH) motif and the leucine zipper (Zip). c-Myc forms a heterodimer through its bHLH-Zip domain with the Max protein (Blackwood and Eisenman, 1991), and a specific DNA binding site (CACGTG) has been identified for the complex (Blackwell et al., 1990; Blackwood and Eisenman, 1991; Blackwood et al., 1992; Halazonetis and Kandil, 1991; Prendergast and Ziff, 1991). A strong and highly conserved transcriptional activation domain is located within the amino terminus of Myc proteins (Kato et al., 1990). Importantly, both the transactivation domain and the DNA binding domain are required for transformation (Stone et al., 1987). In addition to specific transcriptional activation, repression by c-Myc has been described for several genes including c-myc itself, the neu proto-oncogene, and the cyclin D1 gene (Penn et al., 1990a; Philipp et al., 1994; Sun et al., 1991). Together, these data indicate that Myc proteins are transcription factors that affect cellular physiology by altering the expression of key cellular genes, the altered expression which is ultimately responsible for the myc-induced phenotype.

The activity of Myc proteins is tightly regulated by several independent mechanisms. During the process of cellular differentiation, Myc is replaced by Mad or Mxi in the Max complex, generating novel heterodimers that suppress transcription by interacting with the Sin3 repressor (reviewed by Bernards (1995)). In addition, the amino-terminal transactivation domain is regulated in at least two different ways. Phosphorylation of threonine 58 and serine 62 within the transactivation domain has been shown to occur in a cell cycle-regulated fashion (Lutterbach and Hann, 1994), and mutation of these phosphorylation sites affects transactivation and transformation by c-myc (Albert et al., 1994; Gupta et al., 1993; Henriksen et al., 1993; Pulverer et al., 1994; Seth et al., 1991). In addition, the transactivation domain of c-Myc can form a specific complex with the retinoblastoma-related protein p107, resulting in inhibition of c-Myc transactivation (Beijersbergen et al., 1994; Gu et al., 1994).

Activation of the proto-oncogene c-myc by gene amplification, proviral insertions, as well as chromosomal translocation involving the c-myc locus has been described in a number of human tumors. The translocation of the c-myc gene on chromosome 8q24 to immunoglobulin gene loci on chromosome 14q32, 22q11, or 2p12 is considered to be a central molecular event in the pathogenesis of Burkitt’s lymphoma (BL) (Dalla-Favera et al., 1982). Variability in the breakpoint positions distinguish between the subtypes endemic and sporadic (Pellicci et al., 1986). The human c-myc gene is composed of three exons, of which the first is noncoding. Sporadic BLs typically possess breakpoints in the first exon or intron of the c-myc gene, whereas the endemic cases usually have the chromosome 8 breakpoints far 5’ to the c-myc gene. A putative repressor binding site has been identified at the 5’-end of the first exon of c-myc (Siebenlist et al., 1984). Translocations that separate this exon from the rest of the gene as well as accumulated mutations within this region could result in a release of the c-myc
gene from the action of the repressor. Exon 1 mutations have also been found to abrogate the transcriptional attenuation that occurs at the 3'-end of exon 1 (Bentley and Groudine, 1986a, 1986b; Cesaran et al., 1987). Within the first intron of the c-myc gene, a 20-base pair region has been identified as the binding site of a nuclear protein named MIF. This interaction was abrogated by point mutations present in a BL cell line (Zajac-Kaye et al., 1998). Mutations in the same region have also been described for other BL cell lines, supporting the idea that the MIF protein may be an important factor for control of c-myc expression.

Apart from mutations that affect c-myc expression, recently a number of endemic and sporadic BL cell lines and some primary tumors have been reported to have mutations within the protein-encoding exons 2 and 3 of c-myc (Albert et al., 1994; Bhutia et al., 1993; Yano et al., 1993; Clark et al., 1994; Murphy et al., 1986; Rabbits et al., 1983, 1984; Shoewe et al., 1985). In some cases, it has been shown that these mutations are present before the chromosomal translocation takes place, suggesting that mutations within the protein-encoding region of c-myc are an early event in lymphomagenesis (Bhutia et al., 1993). This suggests that the presence of the mutation is not neutral with respect to Myc function but rather that it confers a growth advantage onto the BL tumor cells. This is supported by the finding of several groups that BL-derived mutant c-myc alleles have increased transforming activity in vitro (Frykberg et al., 1987; Henriksson et al., 1993; Hoang et al., 1995).

It has recently been reported that BL-derived mutant c-Myc proteins are resistant to p107-mediated suppression of transactivation (Gu et al., 1994; Hoang et al., 1995). Surprisingly, these mutant c-Myc proteins had a wild type ability to bind p107 (Hoang et al., 1995). It has been suggested that BL-derived mutant c-Myc alleles lack phosphorylation of threonine 58, the phosphorylation of which is dependent on prior phosphorylation of serine 62 by a p107-cdk2 complex. Thus, it has been proposed that in normal cells cyclin A-cdk2 is recruited to the c-Myc transactivation domain by p107, causing it to phosphorylate serine 62. After this has occurred, additional phosphorylation on threonine 58 is possible, leading to down-modulation of c-Myc transactivation (Hoang et al., 1995).

In the present report, we have studied three different BL-derived c-myc point mutants, each described to be the only alteration in the c-myc coding region of the corresponding primary tumor, and one BL-derived c-myc point mutant detected in a cell line. The four mutant c-Myc proteins were analyzed for their ability to transactivate transcription both as GAL4 fusion protein as well as a full-length protein. In contrast to other reports, we find no significant effect of these mutations on c-Myc transactivation and sensitivity to p107 suppression.

**EXPERIMENTAL PROCEDURES**

**Cell Culture and Transfections**—The human osteosarcoma cell line U2-OS and CHO cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum. Transfections were performed using the standard calcium phosphate precipitation technique (Van der Eb and Graham, 1980).

**Plasmid Constructs**—The coding sequence of the human c-myc gene was isolated from pSP64 c-myc (generously provided by J. Woodgett) and cloned into the pBl 31 vector (Morgenstern and Land, 1990) and the pALTER-1 vector (Promega). The c-myc mutants Ser-57, Thr-58, Ser-86, and Leu-115 were made by polymerase chain reaction using the different pJ3-c-myc mutant plasmids as templates. The polymerase chain reaction-amplified c-myc fragments encoding c-myc amino acids 1-262 were cloned into a pl 31 vector containing the GAL4 1-147 coding sequence. The c-myc mutants generated by polymerase chain reaction were verified by DNA sequencing. The expression vectors pCMVp107AS (antisense) and pCMVp107 (sense) were described previously (Zhu et al., 1993). The reporter plasmid with five GAL4 DNA binding sites upstream of a minimal promoter linked to the chloramphenical acetyltransferase (CAT) gene has been described (Kato et al., 1990). The reporter plasmid with four c-MycMax binding sites (CAGCGT), upstream of a minimal promoter linked to the CAT gene, was kindly provided by Dr. R. N. Eisenman (Kretzner et al., 1992).

**CAT Assays**—U2-OS cells or CHO cells on 100-mm dishes were transiently transfected with 5 μg of CAT reporter construct, 0.2 μg of pSV40 luciferase plasmid, 0.5 μg of c-Myc activator plasmid, and 3 μg of either pBl SV107 or pCMVp107AS plasmid as indicated. Where indicated, 3 μg of cdk2-DN was added. The total amount of DNA was made up to 18 μg for each transfection by adding herring sperm DNA. 36-40 h after transfection, cells were collected, and CAT activity was determined using the phase extraction method (Seed and Sheen, 1988). In U2-OS cells, CAT counts were normalized to luciferase activity as determined using the luciferase assay system (Promega). In CHO cells, CAT counts were normalized to protein content using a modified Bradford assay. This procedure was used to precisely replicate the experimental procedure used by Hoang et al. (1995).

**Western Blot Analysis**—For Western blot analysis of transiently transfected cells, total cell lysates were collected from 100-mm dishes 36-40 h after transfection. Lysates were boiled in 200 μl of 2× protein sample buffer. One-half of the lysates was resolved by 10% SDS-polyacrylamide gel electrophoresis and subjected to immunoblot analysis using the polyclonal c-Myc antibody pan Myc (1:10,000 dilution, obtained from Cambridge Research Biochemicals) and a peroxidase-coupled anti-rabbit second antibody (1:10,000 dilution) (Tago). The Western blots were developed using the enhanced chemiluminescence system (ECL, Amersham).

**RESULTS**

**Generation and Expression of Mutant c-Myc Proteins**—A summary of reported mutated c-myc codons detected in BL cell lines and primary tumors is given in Fig. 1. Although the numbers are small, the majority of the mutations result in amino acid substitutions within the amino-terminal transactivation domain of c-Myc. Many of the reported mutations in c-myc were identified in BL cell lines rather than in primary tumors. It has recently been reported that in a BL cell line,
mutations in the \( c-myc \) coding region continue to accumulate during cell culture (Albert et al., 1994). It is therefore not clear whether all of the mutations found in BL cell lines were already present in the primary tumor. To circumvent this potential problem, we selected three mutant \( c-myc \) alleles from primary BL in which only a single missense mutation was present. The mutant \( c-myc \) alleles used were Ser-57, Ser-86, and Leu-115 (Bhatia et al., 1993). We also used the mutant Ala-58 detected in a BL cell line (Albert et al., 1994) and studied by others (Gupta et al., 1993; Henriksson et al., 1993; Hoang et al., 1995; Pulverer et al., 1994). To study the function of these mutant \( c-Myc \) proteins, we generated by site-directed mutagenesis three mutant human \( c-myc \) cDNAs, each containing a single amino acid substitution that corresponds to the mutation found in primary BL.

To study transactivation by the mutant \( c-myc \) alleles, we fused the amino-terminal transactivation domain (amino acids 1-262) of wild type and the four mutant \( c-myc \) alleles to the DNA binding domain of the yeast transcription factor GAL4. In a first experiment, we compared expression levels of the various GAL4-myc chimeric proteins. U2-OS osteosarcoma cells were transiently transfected with the wild type and mutant GAL4-myc expression vectors. After two days, cell lysates were prepared from transfected cells and subjected to polyacrylamide gel electrophoresis. The size-fractionated proteins were transferred to a nitrocellulose filter and detected with a polyclonal Myc antibody. As can be seen in Fig. 2, the Myc antibody detects both endogenous \( c-Myc \) protein (which provides an internal control for protein loading) and the slightly faster-migrating transfected GAL4-myc fusion protein. Fig. 2 also shows that the four mutant GAL4-myc fusion proteins are approximately equally well expressed as GAL4-myc wild type.

Transactivation by GAL4-Myc Fusion Proteins—It has recently been reported that several BL-derived mutant \( c-Myc \) proteins resist suppression of transactivation by p107 (Gu et al., 1994; Hoang et al., 1995). We therefore tested the chimeric GAL4-myc proteins for their ability to activate transcription both in the presence and absence of cotransfected p107. U2-OS osteosarcoma cells were transfected with GAL4-myc expression vectors and a CAT reporter gene that was linked to a core promoter and five upstream GAL4 sites in the presence and absence of p107. Fig. 3A shows that the wild type and mutant GAL4-myc expression vectors did not differ significantly in their ability to activate the GAL4-CAT reporter gene. Cotransfection of p107 expression vector caused a greater than 5-fold inhibition of transactivation of both the wild type and BL GAL4-myc expression vectors. We conclude from this experiment that these BL \( c-myc \) alleles do not differ significantly in their ability to activate transcription and sensitivity to suppression by p107.

These results are in apparent contrast with earlier studies by Hoang et al. (1995) and Gu et al. (1994) who found that ten...
different c-Myc alleles from BL cell lines did resist inhibition by p107. Since Hoang et al. (1995) used CHO cells in their studies, we repeated the experiment shown in Fig. 3A in CHO cells. Fig. 3B shows that all four mutant c-Myc chimeric proteins were equally sensitive to p107 suppression in CHO cells as compared to the human osteosarcoma cells. These data indicate that differences in cell type are not likely to be responsible for the observed difference in sensitivity to p107 suppression.

Transactivation by Full-length BL c-Myc Proteins—In addition to testing GAL4-myc fusion constructs, the corresponding full-length c-myc expression vectors were also tested for their ability to activate transcription and sensitivity to p107 suppression. The reporter plasmid used in these experiments contained four consensus c-Myc/Max DNA binding sites (CACGTG) upstream of a minimal promoter and a CAT reporter gene (Kretzner et al., 1992). The results of this experiment, shown in Fig. 4, indicate that again both BL mutant and wild type c-Myc proteins activate transcription to the same extent. Consistent with their similar transactivation ability, we found that the wild type and mutant c-myc expression vectors were expressed equally in transiently transfected cells (data not shown). Again, no significant differences in susceptibility to p107-induced inhibition of transactivation could be observed for any of the mutant c-Myc proteins compared to the wild type (Fig. 4). Together, our data indicate that the three mutant c-Myc proteins derived from primary BL as well as the mutant derived from a BL cell line do not differ significantly from wild type c-Myc, both with respect to transactivation and sensitivity to suppression by p107.

Sensitivity to Cyclin/cdk Phosphorylation—It has been suggested that p107 inhibits c-Myc transactivation by recruitment of an active cyclin A-cdk2 kinase complex to the amino-terminal transactivation domain. Circumstantial evidence has been presented to indicate that this kinase complex phosphorylates serine 62 within the c-Myc transactivation domain, leading to down-modulation of transactivation. BL-derived mutant c-Myc proteins may therefore escape p107 inhibition of transactivation as a result of mutations that prevent efficient cyclin A-cdk2-dependent phosphorylation of c-Myc (Hoang et al., 1995). We used two approaches to evaluate the possible role of the cyclin A-cdk2 complex in the down-modulation of c-Myc transactivation. First, we used a dominant-negative mutant of cdk2 (cdk2-DN) that effectively inhibits cdk2 kinase activity in transiently transfected cells (van den Heuvel and Harlow, 1993). We argued that if cyclin A-cdk2 would be responsible for down-modulation of c-Myc transactivation by p107, cotransfection of the dominant negative cdk2 expression vector should interfere with inhibition by p107 by preventing c-Myc phosphorylation. Fig. 5 shows that the opposite result was found: cotransfection of p107 and cdk2-DN caused a further inhibition of c-Myc transactivation. This suggests that cyclin A-cdk2 does not contribute to down-modulation of c-Myc transactivation by p107. As a control, we transfected a p107 expression vector in the presence or absence of a cdk2-DN expression vector. Fig. 6 shows that p107 is heterogeneously phosphorylated in transiently transfected U2-OS cells. Cotransfection of cdk4-DN or cdk2-DN strongly inhibited p107 phosphorylation, which results in a decrease in the mobility of p107 in SDS-polyacrylamide gels (Beijersbergen et al., 1995). We conclude from this experiment that cdk2-DN is effective as an inhibitor of endogenous cyclin-cdk complexes in transfected cells.

In a second approach, we used an expression vector that directs the synthesis of an amino-terminally truncated p107 protein. p107-N385 is unable to bind cyclin A-cdk2 complexes (Zhu et al., 1995) and may therefore be unable to inhibit c-Myc transactivation. Fig. 5 shows that p107-N385 was more effective than the wild type p107 protein in suppression of c-Myc transactivation. This result further supports the notion that recruitment of cyclin A-cdk2 to c-Myc by p107 is not required to mediate inhibition of transactivation.
Thus, BL cell lines derived from the same tumor have primary BL but is a secondary phenomenon that BL tumor resistance of c-Myc to p107 suppression is not frequent in different cell types have been used in different reports, all studies report that the transactivation ability of mutant BL c-Myc proteins is either comparable to that of wild type c-Myc or reduced. The lack of BL mutations with increased transactivation ability raises the possibility that mutation of amino-terminal residues may affect some other aspect of c-Myc physiology other than transactivation. One possibility is that some combination of factors contribute to tumor genesis because of a reduced ability to induce apoptosis. That Myc-induced apoptosis depends on amino-terminal motifs within c-Myc has recently been demonstrated (Evan et al., 1992). However, all BL mutant c-Myc protein mutants investigated thus far have unaltered ability to induce apoptosis (Hoang et al., 1995). Another possibility is that transrepression by c-Myc is affected by the BL mutations. That transrepression requires the c-Myc amino terminus is supported by several lines of experimentation (Li et al., 1994; Penn et al., 1990a, 1990b; Philipp et al., 1994). It will therefore be worthwhile to study the effects of BL-derived mutant c-Myc proteins in transrepression assays.

The resistance of BL mutant c-Myc proteins to suppression by p107 is not due to a decreased affinity of the mutant c-Myc proteins for p107 (Hoang et al., 1995). It has been suggested that transactivation by wild type c-Myc is down-modulated by an initial phosphorylation of Ser-62 by a cyclin A-cdk2-p107 complex. Subsequently, additional phosphorylation at Thr-58 is allowed by other kinases that inactivate Myc transactivation. BL-derived mutant c-Myc proteins frequently lack phosphorylation of Thr-58, which renders these mutant c-Myc proteins resistant to inactivation by the cyclin A-cdk2-p107 complex (Hoang et al., 1995). Our data do not support this model for two reasons. First, a mutant of p107 that fails to form a stable complex with cyclin A-cdk2 has wild type ability to suppress c-Myc transactivation (Fig. 5). This indicates that cyclin A-cdk2 plays no role in the p107-mediated down-modulation of c-Myc transactivation. Furthermore, a dominant negative mutant of cdk2 that effectively blocks all cdk2 kinase activity in transiently transfected cells (Fig. 6 and van den Heuvel and Harlow (1993)) did not interfere with inhibition of c-Myc transactivation by p107. This further supports the notion that a cyclin A-cdk2 complex does not play a major role in down-modulation by c-Myc is essential, for its transactivating activity is supported by several lines of evidence. First, deletions within the amino-terminal transactivation domain severely affect c-Myc transformation (Kato et al., 1990; Stone et al., 1987). Furthermore, Barrett et al. (1992) have demonstrated a correlation between the transcriptional transactivation potency of Myc proteins and their ability to transform. The c-Myc protein is phosphorylated in vivo, and several studies have suggested that c-Myc transactivation and transformation is influenced by phosphorylation (Albert et al., 1994; Gupta et al., 1993; Henriksson et al., 1993; Pulverer et al., 1994; Seth et al., 1991). Importantly, the two major phosphorylation sites in the transactivation domain, Thr-58 and Ser-62, and their flanking amino acids are most frequently affected in BL (Fig. 1). This may indicate that phosphorylation of at least some of these sites leads to down-regulation of c-Myc growth-promoting activity. Consistent with this is the finding that v-myc oncogenes frequently contain mutations in these phosphorylation sites (Frykberg et al., 1987; Symonds et al., 1989). In this study, we found no evidence that BL mutations affect c-Myc transactivation (Figs. 3 and 4), and similar results have been obtained by two other groups (Gu et al., 1994; Lutterbach and Hann, 1994), whereas two other groups found that mutation of c-Myc phosphorylation sites leads to reduced transactivation ability (Albert et al., 1994; Gupta et al., 1993). Thus, although different constructs and different cell types have been used in different reports, all studies report that the transactivation ability of mutant BL c-Myc proteins is either comparable to that of wild type c-Myc or reduced. The lack of BL mutations with increased transactivation ability raises the possibility that mutation of amino-terminal residues may affect some other aspect of c-Myc physiology other than transactivation. One possibility is that some combination of factors contribute to tumor genesis because of a reduced ability to induce apoptosis. That Myc-induced apoptosis depends on amino-terminal motifs within c-Myc has recently been demonstrated (Evan et al., 1992). However, all BL mutant c-Myc protein mutants investigated thus far have unaltered ability to induce apoptosis (Hoang et al., 1995). Another possibility is that transrepression by c-Myc is affected by the BL mutations. That transrepression requires the c-Myc amino terminus is supported by several lines of experimentation (Li et al., 1994; Penn et al., 1990a, 1990b; Philipp et al., 1994). It will therefore be worthwhile to study the effects of BL-derived mutant c-Myc proteins in transrepression assays.

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of c-Myc transactivation. A prediction of the model proposed by Hoang et al. (1995) would be that Ser-62 and Thr-58 mutants of c-Myc would have an increased transactivation ability by escaping down-regulation by p107. As was discussed above, this is not found (Gu et al., 1994; Lutterbach and Hann, 1994; Albert et al., 1994; Gupta et al., 1993). We favor the view that p107 binds to the c-Myc transactivation domain to prevent it from interaction with proteins that mediate transactivation. We and others have previously shown that c-Myc can interact with the TATA binding protein, and indeed the p107 binding site on c-Myc appears to overlap with that of the TATA binding protein (Hateboer et al., 1993; Beijersbergen et al., 1994; Maheswaran et al., 1994). It should be noted, however, that this fails to explain why BL mutant Myc proteins bind p107 without being sensitive to its inhibitory effect (Gu et al., 1994; Hoang et al., 1995).

The results in the present paper indicate that escape from p107-induced suppression is not a general consequence for all BL-associated c-Myc mutations. It seems more likely that the heterogeneous BL mutations enhance the growth stimulatory BL-associated c-Myc mutations. It seems more likely that the p107-induced suppression is not a general consequence for all c-Myc would have an increased transactivation ability by es-

Acknowledgments—We thank J. Woodgett and R. N. Eisenman for the gift of plasmids; we also thank C. V. Dang for plasmids and communication of results prior to publication.

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