The c-Myc protein is up-regulated in many different types of cancer, suggesting that a detailed understanding of Myc function is an important goal. Our previous studies have focused on determining the mechanism by which Myc activates transcription using the target gene cad as an experimental model. Previously, we found that Myc activates cad transcription at a post-RNA polymerase II recruitment step and that the Myc transactivation domain interacts with a number of cdk-cyclin complexes. We now extend these studies to determine the role of these cyclin-cdk complexes in Myc-mediated transactivation. We have found that cyclin T1 binding to Myc localizes to the highly conserved Myc Box I, whereas cdk8 binding localizes to the amino-terminal 41 amino acids of the Myc transactivation domain. We showed that recruitment of cdk8 is sufficient for activation of a synthetic promoter construct. In contrast, the ability of Myc to activate transcription of the cad promoter correlates with binding of cyclin T1. Furthermore, recruitment of cyclin T1 to the cad promoter via a Gal4 fusion protein or through protein-protein interaction with the HIV-1 Tat protein can also activate cad transcription. These results suggest that Myc activates transcription by stimulating elongation and that P-TEFb is a key mediator of this process.

The protein product of the c-myc oncogene is a transcription factor that is up-regulated in a number of different types of human cancers, including lymphomas and prostate, colon, liver, and breast tumors (for review, see Refs. 1 and 2). Numerous studies have shown that up-regulation of c-Myc is not simply a consequence of neoplasia but instead is directly involved in the formation of tumors. For example, in tissue culture systems, cotransfection of Myc and activated Ras into rat embryo fibroblasts causes cellular transformation (3). In mouse models, targeted transgenic expression of Myc to specific tissues predisposes the animals to tumor formation (4–7). Interestingly, recent studies have shown a requirement for continual expression of Myc protein for tumor maintenance (8). Furthermore, another study has shown that only a transient decrease in Myc is necessary to inhibit tumor growth (9). Such studies suggest that one way to elicit regression of a tumor containing elevated Myc protein would be to design inhibitors that block Myc function.

It is generally believed that Myc-mediated neoplastic transformation is due at least in part to activation of a set of target genes. Therefore, understanding how Myc functions as a transcription factor will provide insight into how one might inhibit or reverse tumorigenesis. Myc is a member of the basic helix-loop-helix leucine zipper (bHLHzip) family of transcription factors, which bind to a DNA motif called an E box, which has the consensus sequence CACGTG (10). To bind to an E box Myc must form a heterodimer with a protein called Max, another bHLHzip protein (11). A number of studies have attempted to block transactivation by Myc using various methods, including the use of antisense oligonucleotides to block Myc protein synthesis, or the use of peptides or small molecules that prevent Myc from forming heterodimers with Max (12–15). Although at least partially successful as monitored by examination of tumor growth and the levels of specific Myc target genes, such inhibitors may not represent the best approach. Recent studies using microarrays have suggested that Myc may activate hundreds of cellular genes, including many that are required for maintaining cellular homeostasis and basic metabolic functions (16–18). Clearly inhibiting all Myc function, and thus down-regulating all Myc target genes, may be too severe. A more successful approach may be to pick one or several target genes whose expression may contribute to Myc-mediated neoplasia and design an inhibitor that could specifically block Myc-mediated activation of these particular target genes.

We have shown that the gene encoding the trifunctional enzyme carbamoyl-phosphate synthase/aspartate carbamoyltransferase/dihydroorotase, which catalyzes the first three rate-limiting steps of pyrimidine synthesis, is a bona fide Myc target gene. Expression of cad mRNA peaks at the G1/S phase boundary of the cell cycle, and an E box located downstream of the transcription start site of the cad gene is essential for the growth-regulated increase at the G1/S phase boundary (19). Studies using chromatin immunoprecipitation revealed that Myc binding correlates with cad expression in various differentiation and proliferation model systems (20–22). The function of the cad protein makes the cad promoter an attractive target to use as a model system for the development of a selective Myc inhibitor, because pyrimidine synthesis is not needed for cells that are not undergoing DNA synthesis (which is true of many normal, differentiated cells in the adult) but is essential for rapidly dividing tumor cells.

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‡ The abbreviations used are: bHLHzip, basic helix-loop-helix leucine zipper; odc, ornithine decarboxylase; tert, telomerase reverse transcriptase; cad, carbamoyl-phosphate synthase/aspartate carbamoyltransferase/dihydroorotase; TAD, transactivation domain; MBI, Myc Box I; MBII, Myc box II; P-TEFb, positive transcription elongation factor b; RNAP II, RNA polymerase II; CTD, carboxyl-terminal domain; GST, glutathione S-transferase; TAK, Tat-associated kinase; DRB, 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole.
Having selected the cad promoter as a model system, the next step is to determine exactly which regions of the Myc transactivation domain (TAD) are important in activation of this specific promoter. A great deal of work has been previously done to determine the regions of the Myc protein that are important for its transactivation function. For example, Myc amino acids 1–143 can activate transcription when fused to the Gal4 DNA binding domain (29). Contained within this amino-terminal region of Myc are two regions that are highly conserved within c-Myc proteins of many species as well as in N-Myc and L-Myc, proteins related to c-Myc in both structure and function. These two regions are called Myc Box 1 (MBI, amino acids 45–63) and Myc Box 2 (MBII, amino acids 129–143). The role of MBI and MBII in transcriptional activation by Myc is controversial. Numerous studies have suggested that deletion of MBI does not affect the ability of Myc to activate transcription (23, 24). In contrast, MBII has been shown to be required for the interaction of Myc with several proteins that are part of transcription complexes involved in histone acetylation and chromatin remodeling, including TRRAP, TIP48, TIP49, and BAF53 (25–27). Furthermore, several studies using chromatin immunoprecipitation have shown that, at certain Myc target promoters, changes in the levels of histone acetylation correlate with Myc binding and increased transcription, and TRRAP recruitment appears to be involved in this phenomenon (28–30). In contrast, a study examining the ability of Myc to activate transcription in yeast showed that neither MBI or MBII were required to activate transcription and that amino acids 1–41 and 66–127 were able to recruit chromatin remodeling complexes (31). Finally, a recent study showed that MBII is essential for activation of the tert promoter in primary cells, but not in immortalized fibroblasts, whereas MBI is dispensable for Myc-mediated activation of several other Myc target promoters (32). Thus the role of MBI and MBII in mediating the ability of Myc to activate a specific target gene cannot be assumed but must be determined by experimentation.

We have previously shown that amino acids 1–143 of Myc are sufficient to activate the cad promoter. Although this region of Myc can recruit histone acetyltransferases, our previous results indicate that Myc does not function to alter the level of acetylated histones on the cad promoter (33). However, we also showed that Myc 1–143 could interact with several cyclin-cdk complexes involved in transcriptional regulation. Based on our findings that Myc can recruit cyclin-cdk complexes and that the cad promoter is activated at a step subsequent to histone acetylation and RNA II recruitment, we had hypothesized that Myc functions at the cad promoter to recruit a kinase, which phosphorylates the C-terminal domain (CTD) of RNA polymerase II (RNAP II), and stimulate release of a paused RNAP II (33). The goals of this current study are to further investigate this hypothesis by defining the regions of the Myc TAD that bind to various cyclin-cdkks and to determine if these regions are important in the activation of the cad promoter.

**MATERIALS AND METHODS**

**Plasmids**—GST-Myc (1–143) has been described previously (22). The plasmids GST-Myc (1–41), GST-Myc (1–70), GST-Myc (36–70), GST-Myc (1–103), and GST-Myc (1–120) contain the amino acids of human c-Myc indicated in parentheses in the name of each plasmid. The appropriate Myc sequence was obtained by PCR amplification using the plasmid Gal4-Myc (1–262) (a gift from C. Dang) as template with primers containing BamHI restriction sites. The sequences of the primers can be found at our website (www.mearle.oncology.wisc.edu/farnham).

The PCR products were gel-purified, cut with BamHI, and ligated into BamHI-digested pGEX-4T-1.

The plasmids Gal4-Myc (36–70), Gal4-Myc (1–70), and Gal4-Myc (1–120) were cloned in the same manner as the GST fusions, except primers with SacI sites were used for PCR, and digested PCR products were ligated into SacI-digested pSG424 (a gift from C. Dang). The nucleotide sequence of all plasmids was verified by dyeoxy sequencing. The plasmids Gal4-Myc (1–41), Gal4-Myc (103–143), and Gal4-Myc (1–143) were a gift from C. Dang. The plasmids Gal4-cyclin T1 and CMV-cdk9, were a gift from L. Lania. Gal4-cdk8 was a gift from C. Hermann. SVE-cyclin C was a gift from P. Robbins.

**Protein Affinity Chromatography**—HeLa cell nuclear extract was prepared from frozen cells as described previously (34) and was dialyzed against affinity chromatography buffer (10 mM HEPES (pH 7.9), 1 mM EDTA, 1 mM dithiothreitol, 20% glycerol) containing 0.5 mM phenylmethylsulfonyl fluoride and 0.1 M NaCl. GST fusion proteins were prepared and immobilized on glutathione-Sepharose 4B (Amersham Biosciences, Piscataway, NJ) and incubated with HeLa nuclear extract, the columns were washed, and the proteins were eluted as described previously (35). Eluates were analyzed by Western blot analysis with anti-cdk8 sc-1521 and anti-cyclin T1 sc-8128 (Santa Cruz Biotechnology, Santa Cruz, CA) antibodies. Each binding experiment was repeated at least three times.

**Tissue Culture and Transfections**—NIH3T3 cell cultures were maintained and synchronized as previously described (20). For cad-luciferase cotransfections, 1 × 10⁵ cells were cotransfected with 0.5 μg of the indicated reporter plasmid and 2.5 μg of the indicated Gal4 fusion protein expression plasmid. Calcium phosphate transfections were performed as described previously (21).

**RESULTS**

**Identification of the Minimal Regions of the Myc TAD That Bind Cyclin T1 and cdk8**—Our previous work showed that the Myc TAD can recruit several cdk and cyclin proteins in vitro (22). In particular, strong interaction was seen with cyclin T1 and cdk8. Cyclin T1 is a component of P-TEFb, which is composed of the proteins cdk9, a regulatory cyclin subunit (which can be cyclin T1, cyclin T2a, cyclin T2b, or cyclin K), and the 75K small nuclear RNA, which regulates the kinase activity of cdk9 (36–38). Cdk8 heterodimerizes with cyclin C. Cyclin-cdk complexes have been implicated in transcription regulation, and it was possible that either cyclin T1 and its partner cdk9 or cdk8 and its partner cyclin C were important in mediating Myc function at the cad promoter. However, our initial studies used a large domain of Myc, and therefore it was not clear if the binding of either of these proteins precisely correlated with cad transactivation. Therefore, we have now determined the minimal region of the Myc TAD that binds to cyclin T1 and cdk8. To do this, we constructed a series of glutathione S-transferase (GST) fusion proteins consisting of fragments of the Myc TAD fused to GST (Fig. 1). The deletions were designed around the locations of the highly conserved Myc boxes at amino acids 45–63 (MBI) and 129–143 (MBII). To examine binding to the Myc TAD, GST fusions were synthesized in Escherichia coli and immobilized onto glutathione-Sepharose beads. To ensure that the glutathione beads had equal amounts of the GST proteins on them, a fraction of the beads were boiled and loaded onto an SD-S-PAGE gel that was stained with Coomassie Blue to visualize proteins, which showed that approximately equal amounts of protein were bound to the beads (Fig. 2, top). Then,
HeLa nuclear extract was passed over the beads, and, after extensive washing, bound proteins were eluted and analyzed by Western blot with antibodies to cyclin T1 and cdk8. When a Western blot of the eluted proteins was probed with an antibody to cyclin T1, we found that gradual deletion of the C terminus from the Myc TAD gradually reduced binding of cyclin T1. However, binding remained detectable until MBI was deleted (Fig. 2, bottom). Furthermore, cyclin T1 was able to bind a GST fusion containing MBI plus a few additional amino acids (GST-Myc 36–70). Thus we conclude that cyclin T1 binds at or near MBI on the Myc TAD. The gradual reduction in binding observed when increasing numbers of amino acids are deleted could be due to a second binding site for cyclin T1 in the Myc TAD. Alternatively, optimal binding of cyclin T may require that the MBI region be located in a larger amount of the Myc TAD for optimal folding and/or presentation of the binding site.

We also probed a Western blot of proteins bound to the GST fusions with a cdk8 antibody. We found that, like cyclin T1, cdk8 binding gradually was reduced with deletion from the C terminus. However, unlike cyclin T1, cdk8 bound to the first 41 amino acids of the Myc TAD rather than to MBI (Fig. 2, bottom). Thus the interaction sites of cyclin T1 and cdk8 localize to different regions of the Myc TAD.

**The Ability of Myc to Activate cad Transcription Correlates with Binding of Cyclin T1**—Having localized sites of interaction of cyclin T1 and cdk8 on the Myc TAD, we next wished to determine if binding of these proteins correlates with the transcriptional activity of the Myc TAD on the cad promoter. To test this, we made fusions of the Myc TAD deletion constructs to the Gal4 DNA binding domain. We then cotransfected each of these constructs into NIH3T3 cells along with the cad3G4luc reporter, which contains the minimal cad promoter and three Gal4 DNA binding elements in place of the E box. The results of this experiment show that, although activity decreases as the Myc TAD is deleted from the C terminus (Fig. 3A), the Gal4-Myc 1–70 construct, which retains the ability to bind cyclin T1, also retains the ability to activate the cad promoter. However, further deletion leaving only Myc amino acids 1–41 abolishes the ability to activate the cad promoter, although the Gal4-Myc 1–41 construct does retain transactivation potential on other promoters (see below). This suggests that recruitment of cdk8 is not sufficient to activate cad. Finally, it should be noted that MBI, a major site of interaction of Myc with histone acetyltransferase complexes, does not appear to significantly influence the ability of the Myc TAD to activate cad3G4luc (compare Gal4-Myc-(1–143) to Gal4-Myc-(1–120)), a result that has been seen by others on both synthetic and natural promoters (24, 32).

Because Myc amino acids 1–70, but not 1–41, could activate cad, we also investigated the ability of MBI alone to activate cad3G4luc. However, Gal4-Myc-(36–70) could not activate cad3G4luc despite its ability to bind cyclin T1 (Fig. 3A). This could suggest that recruitment of cyclin T may contribute to the ability of the Myc TAD activate transcription, but that it is not sufficient. Alternatively, the failure of Gal4-Myc-(36–70) to activate the cad promoter may be due to technical reasons. Western blot analysis of the transfected Gal4 fusions showed that all of the Gal4 fusion proteins were similarly expressed in NIH3T3 cells, including Gal4-Myc-(36–70) (data not shown). However, the expression data does not rule out the possibility that the Gal4-Myc-(36–70) construct may not fold correctly in the nucleus and thus may not bind cyclin T1 efficiently. Further investigations as to whether recruitment of cyclin T1 is sufficient to activate the cad promoter are described below.

**Transcriptional Activity of Myc 1–41 Depends upon Promoter Context**—We have defined several regions of the Myc TAD that are important for activation of the cad promoter. Because our goal was to identify a region of Myc that might be specifically required for activation of cad (and perhaps other select target genes) but was not required for the activation of all Myc target genes, we repeated the cotransfections using the reporter plasmid pG5TI luc in place of cad3G4luc. pG5TI luc drives luciferase expression via a synthetic promoter containing five tandem Gal4 sites placed upstream of a TATA box and an initiator element (Fig. 3B). Cotransfection of this reporter with the various Gal4-Myc constructs revealed that the ability of these regions of the Myc TAD to activate pG5TI luc was similar to cad3G4luc, with two exceptions. First, the Gal4-Myc constructs activated the pG5TI luc reporter about 2- to 4-fold better than they did cad3G4luc. This could be due to the fact that pG5TI luc contains two more Gal4 sites than cad3G4luc. Second, Myc 1–41 is able to activate pG5TI luc, whereas it cannot activate cad3G4luc. This activation is not due to the general increase in the activity of the Gal4-Myc constructs on pG5TI luc, because when comparing the activity of Myc 1–41 to the full-length Myc TAD, Myc 1–41 has 8% of the activity of Myc 1–143 on cad3G4luc, but Myc 1–41 has 31% of the activity of Myc 1–143 on pG5TI luc. Importantly, this data suggests that recruitment of cyclin T1-cdk9 may be more critical for the activation of cad than for the activation of all Myc target genes.

**Direct Recruitment of Cyclin T1, but Not MBI9, to the cad Promoter Can Substitute for Myc**—Our results from the experiments using portions of the Myc TAD fused to the Gal4 DNA binding domain suggest that cyclin T1-cdk9 but not cyclin C-cdk8 is important for cad transcription. If this is the case, then alternative mechanisms for recruitment of cyclin T1-cdk9 to the cad promoter should also activate transcription. Because cyclins and cdks do not contain a DNA binding domain, they cannot localize to promoter regions without either interactions with or fusion to a DNA binding protein. We have now tested the effects of bringing cyclin T1-cdk9 complexes to the cad promoter using both of these methods, first by using Gal4-cyclin T1 and Gal4-cdk8 to recruit these proteins directly to cad and by using Gal4 fused to another transactivator that binds to cyclin T1-cdk9 (see below). Previous studies using Gal4-cyclin...
T1 and Gal4-cdk8 have shown that these constructs have the ability to activate a number of viral and cellular promoters (39–42). Therefore, we compared the ability of cyclin T1-cdk9 and cdk8-cyclin C to directly activate cad transcription by employing Gal4-cyclin T1 and Gal4-cdk8 fusion proteins. Previous results suggest that cotransfection of full-length cdk9 enhances the ability of Gal4-cyclin T1 to activate transcription (22), so cdk9 was coexpressed with the Gal4-cyclin T1. Similarly, the cyclin partner of cdk8, cyclin C, was coexpressed along with Gal4-cdk8. We found that Gal4-cyclin T1 plus cdk9 can activate cad3G4luc to a similar level as that of Gal4-Myc-(1–143) (Fig. 4A). In contrast, we found that Gal4-cdk8 plus cyclin C were unable to activate cad. However, both cyclin-cdk complexes could activate the pG5TI luc reporter (Fig. 4B). This specificity is similar to that seen when comparing Gal4-Myc-(1–70) (which can recruit cyclin T1) to Gal4-Myc-(1–41) (which can only recruit cdk8). Importantly, these activator bypass experiments indicate that recruitment of cyclin T1, but not cdk8, is sufficient for activation of cad, suggesting that the inability of Gal4-Myc-(36–70) to activate transcription may be a result of technical reasons.

Tat Can Substitute for Myc to Activate the cad Promoter—An unusual feature of the cad promoter is that the Myc binding site is naturally located downstream of the transcription start site at +65. As shown above, activation of Myc by recruitment to this site appears to be due to recruitment of cyclin T1 and cdk9, which are components of P-TEFb. The mechanism by which Myc activates cad is very similar to the way that Tat activates transcription from the HIV-1 promoter. Tat is a protein produced by the HIV-1 virus that is required for efficient transcription of HIV (reviewed in Ref. 43). In the absence of Tat, transcription initiates but halts after synthesis of a few nucleotides of mRNA. Tat binds to a structure on the nascent transcript called the Tat-associated region and stimulates elongation by recruiting a cellular kinase, initially called Tat-associated kinase (TAK), which phosphorylates the RNAP II CTD (44). It was soon discovered that TAK is in fact P-TEFb, and the interaction of Tat and cyclin T1 is responsible for the ability of Tat to activate HIV transcription (45, 46). Therefore, like Myc, Tat binds to an element downstream of the transcription start site, although it binds to RNA rather than DNA, and it activates transcription from the HIV-1 promoter by recruiting P-TEFb.

The similarities between activation of the cad promoter by Myc and activation of the HIV promoter by Tat suggest that Tat may be able to activate transcription from the cad promoter. However, Tat does not contain a DNA binding domain, so it was necessary to use a Gal4-Tat fusion construct to recruit Tat to the cad promoter. Gal4-Tat has been previously shown to activate transcription of reporters containing Gal4 binding sites (47). We cotransfected Gal4-Tat with the reporter plasmid cad3G4luc into NIH3T3 cells. NIH3T3 cells are a mouse fibroblast cell line, and it has been previously shown that Tat cannot interact with mouse cyclin T (48). Therefore, if recruit-
ment of cdk9 and cyclin T1 is a requirement for \textit{cad} transcription, we would expect that Gal-Tat could not activate \textit{cad} in 3T3 cells. Accordingly, we found that, in the presence of only mouse cyclin T1 and cdk9, Gal4-Tat is unable to activate cad3G4luc (Fig. 5). However, if inability to recruit cyclin T1-ckd9 is why Tat can not activate the \textit{cad} promoter, then introduction of human cyclin T1 and cdk9 should allow Tat to activate \textit{cad} transcription in 3T3 cells. Therefore, we next transfected plasmids expressing human cyclin T1 and cdk9 along with Gal4-Tat and cad3G4luc. We found that with coexpression of human P-TEFb, Tat is able to activate cad3G4luc as well as Gal4-Myc-(1–143) does (Fig. 5). Another study has shown that CBP/p300 is also a coactivator for Tat (49). That study showed a requirement for introduction of human p300, but not human P-TEFb, into rodent cells for Tat to activate transcription. However, for the \textit{cad} promoter, introduction of human p300/CBP is not required for Tat to activate transcription in mouse cells. These findings corroborate our previous studies in which we have shown that high levels of acetylated histones H3 and H4 are at the \textit{cad} promoter prior to Myc binding and that Gal4-CBP is unable to substitute for Myc in the activation of the \textit{cad} promoter (22, 33). In summary, our results demonstrate that Tat can substitute for Myc to activate the \textit{cad} promoter and that Tat-mediated recruitment of P-TEFb, but not CBP, is necessary for this activation.

**DISCUSSION**

The results of this study provide strong evidence that P-TEFb is a key coactivator that mediates the ability of Myc to
activate the cad promoter. For example, using GST pull-down assays we show that the MBI region of Myc interacts with cyclin T1, and this same domain is critical for the ability of the Myc TAD to activate cad transcription. Furthermore, recruitment of cyclin T1 to the cad promoter via either a Gal4-cyclin T1 fusion or via interaction of cyclin T1 with Gal4-Tat results in transcriptional activity at a similar level to that seen with Myc recruitment. Thus, we have shown by three ways that recruitment of cyclin T1-cdk9 to the cad promoter can activate transcription. It has also been shown that the C-terminal domain of cyclin T1 interacts with the RNAP II CTD, allowing cyclin T1 to activate transcription from DNA elements upstream of the transcription start site (52). Therefore, we propose that the mechanism by which Myc activates the cad promoter is via a post-initiation phosphorylation of the CTD of the RNAPII, allowing release of a paused RNAP and subsequent transcription elongation.

Although the viral transactivator Tat was the first transcription factor shown to require P-TEFb for activity, P-TEFb has been shown to bind to a number of cellular transcription factors that require P-TEFb for activity, a complex that inhibits elongation (50, 51). It has also been shown that the C-terminal domain of cyclin T1 interacts with the RNAPII CTD, allowing cyclin T1 to activate transcription from DNA elements upstream of the transcription start site (52). Therefore, we propose that the mechanism by which Myc activates the cad promoter is via a post-initiation phosphorylation of the CTD of the RNAPII, allowing release of a paused RNAP and subsequent transcription elongation.

In summary, we have found that P-TEFb is an important coactivator for Myc-mediated transcriptional activation of the cad promoter. This interaction is an appealing target for the screening of small molecules that may be eventually used as inhibitors of Myc function and as possible drugs to treat cancer.

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