B-myb Promotes S Phase and Is a Downstream Target of the Negative Regulator p107 in Human Cells*

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Arturo Sala‡§, Ida Casella‡, Teresa Bellon‡i, Bruno Calabretta‡, Roger J. Watson‡, and Cesare Peschle‡**

From the ‡Thomas Jefferson University, Department of Microbiology and Immunology and Jefferson Cancer Institute, Philadelphia, Pennsylvania 19107, the **Department of Hematology and Oncology, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy, and the I Ludwig Institute for Cancer Research, St Mary's Hospital Medical School, Norfolk Place, London W2 1PG, United Kingdom

The retinoblastoma protein family has been implicated in growth control and modulation of the activity of genes involved in cell proliferation, such as B-myb. Recent evidence indicates that the product of the B-myb gene is necessary for the growth and survival of several human and murine cell lines. Upon overexpression, B-myb induces deregulated cell growth of certain cell lines. Here we show that B-myb overexpression is able to induce DNA synthesis in p107 growth-arrested human osteosarcoma cells (SAOS2). p107 might exert its growth-suppressive activity by regulating B-myb gene transcription. Indeed, p107 down-modulated B-myb promoter activity and drastically decreased E2F-mediated transactivation. Finally, B-myb was able to stimulate DNA synthesis of both stably and transiently transduced human glioblastoma cells (T98G). Altogether, these data provide definitive evidence that the human B-myb protein is involved in growth control of human cells, and that p107 has a significant role in regulating B-myb gene activity.

B-myb has been cloned by virtue of its homology with the c-myb protooncogene (1) and its structure indicates that it may be a transcriptional activator. However, conflicting data have hampered a definitive evaluation of B-myb function(s). Some investigators have provided evidence of transcriptional activation of promoters containing Myb-responsive elements by B-myb (2, 3), whereas others showed that B-myb is unable to transactivate these promoters, acting rather as a repressor of c-myb transcriptional activity (4, 5). A recent report has established that B-myb transcriptional activity is highly dependent on the cell type (6), thus explaining the sharp discrepancies in B-myb-mediated biological effects observed in different systems. It has been clearly shown, however, that B-myb is required for the proliferation of murine fibroblasts, human glioblastoma, human leukemic cell lines, and human neuroblastoma cells (7–10) and that deregulated expression of B-myb induces abnormal cell growth and activation of genes such as cyclin D1 and cdc2 in rodent fibroblasts (7). Consistent with the notion that B-myb may be a regulator of the cell cycle, B-myb expression has been correlated with cell proliferation in different systems and is induced at the G1/S border of the cell cycle (11–14). Furthermore, ectopic expression of the HPV16 E7 transforming protein induces up-regulation of B-myb expression, whereas growth suppression agents like TGF-β or the p53 protein cause down-regulation of B-myb mRNA levels (15–17).

In a recent study it was provided evidence that B-myb can bypass p53-induced Waf1/Cip1-mediated G1 arrest (8). p21Waf1/Cip1 can inhibit G1 cyclin protein kinase and the phosphorylation of pRb (18), suggesting that B-myb may overcome retinoblastoma-associated functions.

The retinoblastoma family comprises three members, pRb, p107, and p130, which share structural and functional characteristics. These proteins all induce growth arrest when overexpressed in certain cell lines and are able to bind the viral transforming protein E1A and the E2F family of transcription factors (19–25). It is notable that p107, but not pRb, can inhibit DNA synthesis of C33A cervical carcinoma cells (25); furthermore, E2F-1 can rescue pRb-mediated growth arrest of SAOS2 osteosarcoma cells, whereas it is ineffective in bypassing a p107 block (25, 26). Recent evidence indicates that p107 and pRb may associate in vivo with specific E2F proteins (we will use the term E2F to indicate all the possible members of the family); pRb has been found associated in cell extracts with E2F1, E2F2, and E2F3 (27), whereas p107 seems to bind specifically E2F4 (19, 22). However, when E2F1 and p107 are transiently transfected an interaction can be observed (19), suggesting that weak binding between p107 and E2F1 may also exist in vivo but can be detected only by overexpression. There is mounting evidence that E2F and the associated pRb family proteins are involved in cell cycle regulation of B-myb transcription (14, 15, 28). Thus, a conserved E2F site is located in the human and mouse B-myb promoters within a region specifying the multiple 5′ termini of the mRNA. It has been proposed that specific E2F-p107 and E2F-p130 complexes repress transcription in G0/G1 through binding to this site; induction of B-myb transcription at the G0/G1 boundary, which appears to arise predominantly by a derepression mechanism, correlates with modification of these complexes by cyclin A/Cdk2 association (14, 15). Further evidence that that p107 is responsible for transcription repression in murine NIH 3T3 fibroblasts was provided by the finding that induction of B-myb transcription by HPV E7 protein mutants correlated with their ability to bind p107 rather than pRb (15). These findings indicate that B-myb may be a downstream target of p107 and, as such, suggest a mechanism by which this protein may act as growth suppressor. To provide

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‡§ To whom correspondence should be addressed: Thomas Jefferson University, Dept. of Microbiology and Immunology and Jefferson Cancer Institute, 233 S. 10th St., Philadelphia, PA 19107. Tel.: 215-955-1763; Fax: 215-923-0249.

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The abbreviations used are: pRb, the product of the retinoblastoma gene; CMV, cytomegalovirus; HPV, human papilloma virus.
further evidence for this hypothesis, we have investigated the functional relationship among B-myb, p107, and pRb in human cells.

MATERIALS AND METHODS

Cell Lines—The human cell lines SAOS-2, T98G, GM47, and B-myb derivatives were routinely maintained and transfected as described previously (7, 8).

Plasmids—The pCMV-B-myb and pCMV-B-myb mutant and the pCMV-based p107, pRb, E2F1, E2F4, DP-1, and CD20 plasmids were all described. (8, 22, 24, 25, 29). The pGLHB-B-myb, containing the human B-myb promoter driving the luciferase gene, has been described (14).

Cell Cycle Analysis—DNA content in the B-myb rescue experiments was analyzed by fluorescence-activated cell sorting. Briefly, 2 μg of the plasmid pCMV-CD20 were cotransfected with 0.5, 5, or 10 μg of pCMV-p107 or pCMV-pRb constructs and 10 μg of the wild type or mutant B-myb constructs in SAOS-2 cells. 48 h after transfections, cells were collected and stained with fluorescein isothiocyanate-labeled anti-CD20 antibody followed by propidium iodide staining, as described (25). For cell cycle studies performed in T98G cells, 5 μg of pCMV-CD20 plasmid were cotransfected with 20 μg of pCMV-B-myb or pCMV-empty plasmid. After 48 h, cells were collected and analyzed as described above.

Cell cycle analysis of the GM cell lines was performed after 4 days of starvation in 0.5% fetal calf serum and subsequent restimulation with 10% fetal calf serum. At the end of the time-course the cells were fixed with 70% ethanol, labeled with propidium iodide, and analyzed by fluorescence-activated cell sorting using the software program Multi-cycle (Phoenix Flow Systems).

Transient Transfections and Luciferase Assay—Transient transfections were carried out according to the calcium phosphate precipitation method (30). Briefly, 5 μg of B-myb promoter driving the luciferase cDNA were cotransfected with 1 μg of CMV-based constructs containing E2F1, E2F4, DP-1, pRb, and p107 in 10-mm dishes containing 2–5 × 10^5 cells each. Transfection efficiency was checked by adding 1 μg of pSV-β-gal plasmid in each experimental point. Luciferase assays were performed using 5–10 μl of total cell lysate (600 μl/dish), depending on β-galactosidase activity. Lysates were mixed with the luciferase substrate following the manufacturer’s instructions (Promega). Luciferase activity was measured with the aid of a scintillation counter.

Western Blot—36 h after transfection 5 × 10^5 cells were lysed in SDS sample buffer, boiled, and loaded onto a 4–15% gradient acrylamide minigel (Bio-Rad). After electrophoresis, the proteins were electroblotted onto nitrocellulose, and the filter was incubated with peroxidase-labeled secondary antibody (1:1000 dilution of monoclonal antibody XZ-37 (a kind gift of Dr. G. Condorelli), which recognizes the same epitope in both p107 and pRb. After several washes in phosphate-buffered saline, 0.1% Nonidet P-40 the filter was incubated with peroxidase-labeled secondary antibody and washed, and the signal was detected using the ECL reagent (Amersham Corp.).

RESULTS

B-myb Rescue of p107-induced G1 Block—A large segment of the human and murine B-myb promoters share a high degree of homology and a site that has been shown to bind E2F, suggesting that the mechanism of B-myb transcriptional control involving E2F and its partners is evolutionarily conserved. B-myb promoter activity peaks during the S phase of the cell cycle, and in both the murine and human systems, p107 can be detected in a cell cycle-regulated manner bound to the E2F site (14, 15, 28). To investigate the possibility that a functional link exists between p107 expression and B-myb activity, we co-transfected increasing amounts of CMV-driven p107 and pRb in SAOS-2 cells, which have been shown to be sensitive to the suppressive action of both proteins, and an expression vector driving B-myb. A CMV-CD20 plasmid was included in each transfection, and cells positive for CD20 were subjected to fluorescence-activated cell-sorting analysis. As expected, increasing amounts of both p107 and pRb resulted in a reduction in the number of cells traversing the S phase. However, when 10 μg of B-myb expression vector were added to the transfection mixtures containing p107, a significant increase in the percentage of cells in S phase was observed (Fig. 1A), whereas B-myb lacked any activity in pRb-blocked cells (Fig. 1B). A B-myb mutant lacking the DNA-binding domain was without effect (Fig. 1A), suggesting that the DNA-binding function is required in the rescue activity. Surprisingly, overexpression of B-myb did not affect cell cycle distribution of SAOS2 cells (Fig. 1A, and data not shown), although it could alter the growth characteristics of T98G cells (see below), indicating that B-myb promotion of cell growth is cell type-specific and that the rescue of p107 is not due to a nonspecific growth-related effect.

The possibility that B-myb might neutralize p107 by protein-protein interaction was explored in vivo by co-transfecting B-myb and p107 expression vectors in SAOS2 cells, followed by immunoprecipitation with p107 antibody and Western blot with a B-myb-specific antibody. No association was found between B-myb and p107, although we cannot exclude the possibility that a weak or unstable interaction went undetected due to the limits of this technique (data not shown).

p107 Efficiently Represses E2F-mediated Transactivation of the B-myb Promoter—The rescue experiments demonstrated that there is a functional interaction between B-myb and p107. We speculated that B-myb can rescue a p107-induced G1 block because p107 function might be related to the inactivation of B-myb gene transcription, that is B-myb may be a downstream target of p107. In order to address this hypothesis directly, we co-transfected a luciferase vector driven by the human B-myb promoter and CMV-driven E2F1, E2F4, DP-1, and various retinoblastoma family members in different combinations. E2F1 induced a dramatic increase in luciferase activity when co-transfected with the B-myb promoter (Fig. 2A). E2F1-induced transactivation of the B-myb promoter in SAOS-2 cells was several times greater than that observed previously in the HaCaT cell line (14), perhaps reflecting the lack of functional pRb and very low levels of p107 and p130 in SAOS2 cells (Fig. 3, and data not shown). p107 caused a significant decrease (>10 fold) of E2F1-induced transactivation of the B-myb promoter, whereas pRb caused a 3–4-fold reduction (Fig. 2A). This effect was reproduced in three independent experiments, and a Western blot performed after transient transfection revealed that p107 and pRb proteins were both expressed at high levels, although pRb appeared to be more abundant than p107 (Fig. 3). E2F4-induced transactivation of the B-myb promoter was very weak as compared with that induced by E2F-1 (3–4-fold versus >300-fold), and required the presence of DP-1 (Fig. 2B). Significantly, the B-myb promoter activity was repressed substantially by co-transfection with either p107 or pRb alone (Fig. 2C). Thus, it is suggested that these proteins can affect transcriptions of B-myb by endogenous factors, consistent with the notion that B-myb is a downstream target of these negative regulators.

B-myb Induces G2/S Transition in Human Glioblastoma Cells—The fact that B-myb can partially overcome p107-induced growth arrest suggests that B-myb can interfere with the cell cycle machinery of human cells. To investigate in detail the influence of B-myb on cell cycle progression we took advantage of the human glioblastoma cell line T98G, whose proliferation is strictly regulated by serum. After 4 days in medium containing 0.5% serum, approximately 90% of T98G cells were found blocked in G0, feeding the cells with 10% serum causes the cells to undergo a synchronous round of replication. The cell cycle profiles of T98G cells constitutively expressing a transfected B-myb gene were found to differ markedly from parental cells upon reentry into cycle. Thus, the number of cells traversing the G2/S border was significantly higher in T98G cells constitutively expressing B-myb. In fact, after 24 h of serum stimulation, 8% of cells overexpressing B-myb were in G2, and most of the cells appeared to reside in S phase (88.5%), with only 3.4% cells having reached G2. In contrast, the parental cell line
showed a percentage of cells in G1 of 35%, with 52.2 and 12.8% of cells in S and G2, respectively (Fig. 4, A and B). This experiment was repeated with additional clones with identical results.

We also co-transfected T98G cells with pCMV-B-myb and the pCMV CD20 plasmids followed by cell cycle analysis after 48 h. Enforced expression of B-myb in asynchronously growing cells reduced the percentage of cells in G1, while the percentage of cells in S phase was increased (Table I). Although the extent of S phase induction in this experiment does not appear to be dramatic, we should consider that at the time of transfection these cells are actively proliferating and that the degree of stimulation is comparable with that obtained by ectopic expression of E2F4 in SAOS2 cells under similar experimental conditions (19).

**DISCUSSION**

Recent evidence indicates that the different products of the retinoblastoma family participate in cell cycle control, performing similar yet distinct functions as the cell progresses from G1 to mitosis. A model has been developed that shows, depending on the phases of the cell cycle, different retinoblastoma family members in association with E2F. The complexity is even greater if we take into account that five different E2F genes...
have been cloned, whose encoded products can interact with two and maybe more DP proteins (27). It has been shown that several growth-regulated genes contain an E2F site located in close proximity to the transcription start site (31). Some, but not all, of these promoters are activated by E2F1 (14, 30) and it is thought that interaction of E2F with retinoblastoma family members can repress E2F-induced transactivation, switching the E2F site from a positive to a negative element (28, 32).

The rationale of the present study is based on experiments that demonstrated the presence of cell cycle-regulated complexes containing distinct retinoblastoma family members bound to the E2F site of the human and mouse B-myb promoters. In particular, it was shown that p107 containing complexes present during G1 and S phase on the murine B-myb promoter are disrupted by the E7 oncoprotein, resulting in the activation of B-myb transcription (15). These experiments suggested that p107 might be specifically required to modulate growth-regulated activity of the B-myb promoter and that p107-induced growth arrest may be due, at least in part, to repression of B-myb transcription. B-myb is required for the proliferation of several human and murine cell lines, it is broadly expressed, and its overexpression induces altered growth characteristics of murine Balb/c 3T3 cells (7). We have therefore investigated the possibility that B-myb and p107 may be functionally linked.

B-myb overexpression induces S phase in cells that have been blocked by p107 (Fig. 1A); this effect seems to be specific because B-myb cannot rescue the block induced by pRb (Fig. 1B). To test directly the hypothesis that p107 may be involved in the control of B-myb transcription, we analyzed the activity of the human B-myb promoter in the presence of E2F in combination with p107 or pRb. The human B-myb promoter is activated during the G1/S transition of the cell cycle, whereas it is silent during G0 and early G1 (14). We found that p107 was more effective than pRb in the inhibition of E2F1-mediated activation of the B-myb promoter (Fig. 2A). This effect is even more impressive if we take into account that pRb is expressed at higher levels than p107 in transiently transfected SAOS2 cells (Fig. 3). On the other hand, both p107 and pRb appeared to possess similar activity in the inhibition of E2F4-induced transactivation, which was very weak with respect to that of E2F1 (Fig. 2B). Based on these experiments and previous data, we can hypothesize that E2F1 and/or other G1/S-induced E2Fs are involved in the activation of the B-myb gene during S phase, whereas E2F4, which is thought to be associated with the G2/M transition of the cell cycle (33), might rather be involved in the repression of B-myb expression during G0 and early G1.

The evidence provided in this study strongly suggests that p107 might be required to modulate E2F-mediated activation of the B-myb promoter. There is no indication to date of a direct interaction between p107 and E2F1 in vivo, although these proteins do associate when overexpressed (19). Our finding that p107 was more efficient than pRb in the inhibition of E2F1-mediated transactivation of a physiological promoter (B-myb) might be the consequence of enforced expression of the retinoblastoma family members; alternatively, it would suggest that the weak interaction between p107 and E2F1 is functionally relevant. An important finding in this study was that B-myb promotes S phase in a human cell line, thus defining a cause/effect relationship between B-myb expression and DNA synthesis. In fact, B-myb overexpression induced lengthening of the S phase and thus massive accumulation of glio-
blastoma cells in this phase after the addition of serum (Fig. 4); B-myb was not able to override the G0 arrest imposed by serum deprivation, indicating that its function can be exerted exclusively during S phase. At least some B-myb functions appear to be cell type-dependent; overexpression of B-myb did not induce enhanced proliferation of SAOS2 cells, nor of other murine cell lines (34). Indeed, in a recent report it was shown that B-myb transcriptional activity is cell type-dependent and requires a specific co-factor (6).

Three different classes of growth suppressor agents (p107, p53, and TGF-β) seem to target expression levels of the B-myb gene (Fig. 2 and Refs. 8, 13, and 16). Conversely, overexpression of B-myb in human tumorigenesis. The mechanism(s) underlying the positive action of B-myb on cell cycle progression probably rests in the activation of genes required for DNA synthesis. We previously showed that B-myb induces up-regulation of genes involved in cell cycle control such as cyclin D1 and cdc2 in murine Balb/c 3T3 cells (7). Cyclin D1 is required for cell proliferation and, when overexpressed, shortens the G1 phase of the cell cycle (35, 36), whereas cdc2 is required for DNA synthesis and mitosis (37, 38). The identification of B-myb molecular targets would represent the next step needed in understanding its role in the regulation of the cell cycle.

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REFERENCES

1. Nomura, N., Takahashi, M., Matsui, M., Ishii, S., Date, T., Sasamoto, S., and Ishizaki, R. (1988) Nucleic Acid Research 16, 11075–11089
2. Mizuguchi, G., Nakagoshi, H., Nagase, T., Nomura, N., Date, T., Ueno, Y., and Ishii, S. (1990) J. Biol. Chem. 265, 9280–9284
3. Nakagoshi, H., Kanet-Ishii, C., Sawazaki, T., Mizuguchi, G., and Ishii, S. (1992) Oncogene 7, 1233–1240
4. Foss, G., Grimm, S., and Klempauer, K. H. (1992) EMBO J. 11, 4619–4629
5. Watson, R. J., Robinson, C., and Lam, E. W. F. (1993) Nucleic Acids Res. 21, 267–272
6. Tashiro, S., Takemoto, Y., Hando, H., and Ishii, S. (1995) Oncogene 10, 1699–1707
7. Sala, A., and Calabretta, B. (1992) Proc. Natl. Acad. Sci. U.S.A. 89, 10415–10419
8. Lin, D., Fisella, M., O’Connor, P. M., Jadzian, J., Chen, M., Luo, L. L., Sala, A., Travali, S., Appella, E., and Mercer, W. E. (1994) Proc. Natl. Acad. Sci. U.S.A. 91, 10079–10083
9. Arusua, M., Introna, M., Passerini, F., Manovani, A., and Golay, J. (1992) Blood 79, 2708–2716
10. Roschalla, G., Negroni, A., Sala, A., Pucci, S., Romeo, A., and Calabretta, B. (1995) J. Biol. Chem. 270, 8540–8545
11. Arusua, M., Luchetti, M. M., Erba, E., Golay, J., Rambaldi, A., and Introna, M. (1991) Blood 83, 1776–1784
12. Golay, J., Capucchi, A., Arusua, M., Castellano, M., Rizzo, V., and Introna, M. (1991) Blood 77, 149–158
13. Lam, E. W. F., Robinson, C., and Watson, R. J. (1992) Oncogene 7, 1885–1890
14. Lam, E. W. F., Bennett, J. D., and Watson, R. J. (1995) Gene (Amst.) 160, 277–281
15. Lam, E. W. F., Morris, J. D. H., Davies, R., Crook, T., Watson, R. J., and Vousden, K. H. (1994) EMBO J. 13, 871–878
16. Satterwhite, D. J., Aakre, M. E., Gorska, A. E., and Moses, H. L. (1994) Cell Growth & Differ. 5, 789–799
17. Lin, D., Shields, M. T., Ullrich, S. J., Appella, E., and Mercer, W. E. (1992) Proc. Natl. Acad. Sci. U.S.A. 89, 9210–9214
18. Harper, J. W., Adami, G. R., Wei, N., Keyomarsi, K., and Elledge, S. J. (1993) Cell 70, 805–816
19. Beijersbergen, R. L., Kerkhoven, R. M., Zhu, L., Carlee, L., Mathijis, F. M., and Bernards, R. (1994) Genes & Dev. 8, 2680–2690
20. Claudio, P. P., Howard, C. M., Baldi, A., De Luca, A., Fu, Y., Condorelli, G., Sun, Y., Colburn, N., Calabretta, B., and Giordano, A. (1994) Cancer Res. 54, 5556–5560
21. Even, M., Xing, Y., Lawrence, J. B., and Livingston, D. M. (1991) Cell 66, 1155–1164
22. Ginsberg, D., Vairo, G., Chittenden, T., Xiao, Z. X., Xu, G. F., Wynder, K. L., and Caprio, J. A. (1991) Cancer Res. 51, 10415–10419
23. Sathy, J. D., Wang, N. P., Qian, Y. W., Lee, E. Y. H., and Lee, W. H. (1991) Cell 67, 293–302
24. Kaelin, W. G. J., Krek, W., Sellers, W. R., De Caprio, J. A., Achenbaum, F., Fuchs, C. S., Chedel, P., Li, Y., Farnham, P. J., Binan, M. A., Livingston, D. M., and Flemington, E. K. (1992) Cell 70, 351–364
25. Zhu, L., van den Heuvel, S., Helin, K., Fattaey, A., Even, M., Livingston, D. M., Dyson, N., and Harlow, E. (1993) Genes & Dev. 7, 1111–1125
26. Qin, X. Q., Livingston, D. M., Ewen, W., Sellers, W. R., Arany, Z., and Kaelin, W. G. (1995) Mol. Cell. Biol. 15, 742–755
27. Wu, C. L., Zuberer, K. G., Nguw, C., Harlow, E., and Lee, J. A. (1995) Mol. Cell. Biol. 15, 2536–2546
28. Lam, E. W. F., and Watson, R. J. (1993) EMBO J. 12, 2705–2713
29. Helin, K., Wu, C. L., Fattaey, A. R., Lees, J., Dynlacht, B. D., Nguw, C., and Harlow, E. (1993) Genes & Dev. 7, 1850–1861
30. Sala, A., Nicolaides, N., Engelhard, A., Bellon, T., Lawe, D. C., Arnold, A., Grana, X., Giordano, A., and Calabretta, B. (1994) Cancer Res. 54, 1402–1406
31. Nevin, J. R. (1993) Science 258, 424–429
32. Weintraub, S. J., Prater, C. A., and Dean, D. C. (1992) Nature 358, 259–261
33. Vairo, G., Livingston, D. M., and Ginsberg, D. (1995) Genes & Dev. 9, 186–191
34. Lyon, J., Robinson, C., and Watson, R. (1994) Crit. Rev. Oncog. 5, 373–388
35. Baldin, V., Lukas, J., Marcote, M. J., Pagano, M., and Draetta, G. (1993) Genes & Dev. 7, 812–821
36. Quelle, D. E., Ashmun, R. A., Shurtleff, S. A., Kato, J., Bar-Sagi, D., Rousel, M. F., and Sherr, C. J. (1993) Genes & Dev. 7, 1559–1571
37. Furukawa, Y., Piwnica-Worms, H., Ernst, T. J., Kanakura, Y., and Griffin, J. D. (1990) Science 250, 805–808
38. Van den Heuvel, S., and Harlow, E. (1993) Science 262, 2050–2054
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