B-Myb, Cancer, Senescence, and MicroRNAs

Ivan Martinez¹ and Daniel DiMaio¹,²

Abstract

The transcription factor B-Myb plays a critical role in regulating gene expression and is implicated in controlling carcinogenesis and cellular senescence. Transcription of the B-Myb gene is regulated by retinoblastoma proteins acting directly on the B-Myb promoter. Recently, we found that microRNAs also control the abundance of B-Myb mRNA during senescence, adding another level of complexity to B-Myb regulation. This review focuses on the importance of B-Myb in cancer and senescence, with an emphasis on the regulation of B-Myb expression and activity. Cancer Res; 71(16); 5370–3. ©2011 AACR.

Introduction

The v-Myb myeloblastosis viral oncogene homolog (avian)-like 2 (MYBL2; B-Myb) encodes a transcription factor that regulates the expression of numerous genes during cell cycle progression (1). The Myb gene family of transcription factors is present in all vertebrates (2). c-Myb is the homolog of the v-Myb oncogene, which is present in avian retroviruses that cause acute leukemia (3, 4). The other 2 family members, A-Myb and B-Myb, were cloned on the basis of homology to c-Myb (5). In mammals, c-Myb and A-Myb expression is restricted to specific cell types and stages of development, whereas B-Myb is expressed in virtually all proliferating cells (2, 5). In cultured cells, B-Myb expression is highest in the S-phase of the cell cycle, and changes in B-Myb expression have been linked to growth arrest, apoptosis, carcinogenesis, and senescence (6, 7). Thus, it is essential to determine the mechanisms that regulate expression of this important gene.

B-Myb Regulates Genes Important in Cell Proliferation and Survival

All 3 Myb proteins bind to consensus Myb-binding sites (MBS) in DNA (2), but the phenotypes of knockout mice that lack individual Myb family members are strikingly different, with mice lacking B-Myb dying very early in development because the blastocyst inner cell mass does not form (8). These diverse phenotypes show that the Myb proteins carry out different biological functions. Divergent function of the Myb proteins was also suggested by expression profiling, which revealed that ectopic expression of each of the 3 Myb proteins activates different sets of genes (9). B-Myb stimulates transcription of genes that promote entry into the S- and M-phases of the cell cycle (1, 6). For several of these genes, such as DNA topoisomerase IIα and c-Myc, B-Myb acts by binding directly to MBSs in their promoters (see refs. 10, 11). B-Myb activates the expression of other genes that lack MBSs, including B-Myb itself, by interacting with transcription factors that bind to the promoters of these genes (12, 13). In conjunction with E2F proteins, B-Myb also stimulates the expression of genes required for the G2 to M-phase of the cell cycle (14). In addition, binding of B-Myb to the multiprotein LINC/DREAM complex regulates the ability of this complex to affect gene expression (15–18). B-Myb can also negatively repress gene expression, perhaps by competing with other transcription factors whose binding sites overlap with MBSs in target promoters (see refs. 19, 20). Finally, B-Myb associates directly with clathrin and filamin, components of the mitotic spindle (21). The absence of B-Myb reduces the amount of clathrin in the spindle and causes mitotic arrest.

The transcriptional activity of B-Myb is regulated by post-translational modifications and by interactions with other proteins (1). B-Myb is activated by phosphorylation and acetylation, which release it from transcriptional corepressors (22, 23). However, phosphorylation also leads to ubiquitylation of the B-Myb protein (24), decreasing its half-life and limiting its activity to S-phase. B-Myb activity is also regulated by binding to transcriptional coactivators, corepressors, and other proteins (reviewed in ref. 6).

B-Myb in Cancer and Senescence

Given the provenance of c-Myb as a cellular proto-oncogene and the ability of B-Myb to regulate the expression of cell cycle genes, it is not surprising that B-Myb is involved in cell proliferation and carcinogenesis. B-Myb expression is required for entry into S-phase and can overcome growth inhibitory signals (25–27). Cytogenetic analysis of several types of cancers revealed amplification of chromosome 20q13, where B-Myb is located (see ref. 28). In addition, B-Myb overexpression...
occurs in several cancers and has been linked to aggressive tumor growth and poor outcomes in neuroblastomas and other tumors (28–30). Conversely, B-Myb repression can inhibit the proliferation of normal and tumor cells (11, 26, 31, 32). The ability of B-Myb to increase the expression of anti-apoptotic genes such as Bcl2, survivin, and clusterin also contribute to cancer progression (17, 33–35). Interestingly, certain inherited sequence variants of B-Myb are associated with altered cancer risk (30, 36).

Cellular senescence, a form of irreversible growth arrest, seems to be an important obstacle that cells must bypass during carcinogenesis (37). Because B-Myb expression is strongly repressed during senescence, it seems reasonable that loss of B-Myb expression may play an important role in senescence. Several findings support this hypothesis. Repression of B-Myb inhibits proliferation of mouse BALB/c 3T3 fibroblasts, whereas constitutive B-Myb expression allows the cells to grow with reduced growth factors (32). In primary mouse embryonic fibroblasts, overexpression of the ras oncogene induces premature senescence, but coexpression of c-Myc itself is an E2F-responsive gene repressed by the Rb pathway during senescence (42). However, direct repression of these genes (40) allows a population of cells to escape Rb-induced senescence, showing the importance of miR-29 and miR-30 in this process.

These experiments show the complexity of B-Myb regulation during Rb-induced senescence (Fig. 1). Activation of the Rb pathway mobilizes p107 and p130, which, in complex with E2F2, bind to the B-Myb promoter and inhibit transcription. In addition, Rb activation increases the expression of miR-29 and miR-30, which bind to B-Myb mRNA and destabilize it. As noted above, B-Myb is also regulated at the protein level by posttranslational modification and association with other cellular proteins. Presumably, this 3-tiered regulation of B-Myb evolved to ensure profound inhibition of B-Myb activity and complete blockade of cell cycle progression.

miR-29 and miR-30 affect the expression of numerous genes in addition to B-Myb, and many of these targets may also play a role in senescence or carcinogenesis. For example, Fabbri and colleagues have identified DNA methyltransferase 3A and 3B as targets of miR-29 (44). Similarly, in addition to miR-29 and miR-30, numerous microRNAs are upregulated during senescence (41). These microRNAs may also regulate the expression of genes involved in senescence.

Conclusions and Perspectives

B-Myb exerts powerful effects on cell behavior. The multitude of B-Myb protein partners and target genes allows it to regulate many important cellular processes, including proliferation, senescence, apoptosis, and mitosis. On the basis of this spectrum of activities and the association of B-Myb with human cancer, it may be possible to exploit B-Myb as an important prognostic, diagnostic, and therapeutic tool. Do mutations that affect the binding of Rb proteins to the B-Myb promoter or the binding of microRNAs to B-Myb mRNA affect cancer risk by regulating levels of B-Myb? Is the presence of such mutations or the level of B-Myb itself an informative biomarker? Is it possible to influence the activity of B-Myb and affect cellular behavior by modulating its expression or its ability to bind to DNA or its protein partners, including components of the LINC/DREAM
complex and the mitotic spindle? Can as-yet- unrecognized layers of complexity in the regulation of B-Myb be exploited therapeutically? The central role played by B-Myb in cellular proliferation and related processes suggests that the factors that regulate the expression and activity of B-Myb deserve special scrutiny in attempts to develop rational approaches to control cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Joan Steitz and members of the DiMaio laboratory for critical reading of the manuscript.

Grant Support

Work conducted in the authors’ laboratory was supported by a grant from the National Cancer Institute (CA016038).

Received March 28, 2011; revised May 6, 2011; accepted May 12, 2011; published online August 9, 2011.

References
