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Myb protein specificity: evidence of a context-specific transcription factor code

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Abstract

Vertebrates express three different Myb family transcription factors, A-Myb, B-Myb, and c-Myb, that share a highly conserved DNA binding domain, bind to the same DNA sequences, and activate the same reporter gene constructs in transfection assays. However, the three Myb proteins have completely different biological roles, and microarray assays have shown that ectopic expression of each protein causes the activation of different sets of human genes. Furthermore, the genes that are activated by each protein in different cell types are distinct, suggesting that Myb transcription factors are subject to context-specific regulatory mechanisms. The data support a modification code model in which Myb proteins become decorated with different sets of posttranslational modifications in different cell types, and these modifications control the ability of the Myb proteins to interact with other cellular components that are required for activating specific sets of genes.

Introduction

The c-myb protooncogene is the cellular progenitor of the oncogene v-myb, the transforming component of two different avian leukemia viruses, avian myeloblastosis virus (AMV) and E26, both of which transform immature myeloid cells in tissue culture and induce leukemias in chickens [1]. The murine c-myb gene is a common site of retroviral insertions causing leukemia [2–9] and transgenic expression of v-myb induces lymphoid or myeloid tumors in mice [10–13]. In humans, the c-myb gene is localized on human chromosome 6q22-q23 and several types of evidence suggest that overexpression or activation of the c-myb gene is important for tumorigenesis. The c-myb gene is expressed in nearly all human leukemias and lymphomas [14–18] and rearranged or amplified c-myb genes have been found in a variety of leukemias, lymphomas, or cell lines derived from hematopoietic tumors [18–20]. Many other human tumors have also been found to have rearranged or amplified c-myb genes, including colon tumors [21], glioblastomas [22], pancreatic tumors [23], and BRCA-1 mutated breast tumors [24].

The c-myb gene is expressed at relatively high levels in all immature, proliferating hematopoietic cells, including erythroid, myeloid, and lymphoid lineages [25,26], and a functional c-myb gene is required for definitive hematopoiesis [27]. Constitutive expression of c-myb can block the differentiation of immature hematopoietic cells [26,28–33], and antisense oligonucleotides that target c-myb can disrupt the differentiation and proliferation of hematopoietic cells [34–36]. However, c-myb is not expressed in mature, nonproliferating cells, suggesting that it plays a role in promoting proliferation or regulating differentiation or both [1].

The c-myb gene is also highly expressed in other types of immature, proliferating cells, such as the rapidly dividing cells in the colon, where it plays a role in regulating epithelial cell proliferation, differentiation, and apoptosis [37,38]. The c-Myb gene has been found to be amplified in estrogen receptor-positive breast cancer cells [24,39], and expression of the c-myb gene is up-regulated during estrogen-induced proliferation [40,41].

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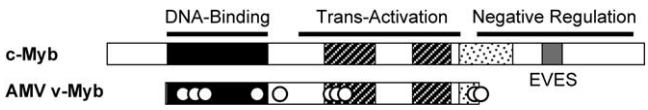

Fig. 1. Structures of c-Myb and v-Myb. The conserved functional domains of the 642 aa long c-Myb protein are shaded and labeled at top. The shaded boxes represent the most conserved domains among chicken, mouse, and human proteins. The EVES domain located near the C-terminus of c-Myb has been shown to be involved in autoinhibition of c-Myb activity. Relative to c-Myb, the AMV v-Myb protein is truncated at both ends (aa 72–444) and has a number of point mutations, indicated by circles, all of which affect its transformation activity.

Structures and functions of Myb proteins

The c-Myb protein is a DNA binding transcriptional activator with a highly conserved structure that includes an N-terminal DNA binding domain, central transcriptional activation domain and C-terminal negative regulatory domain (Fig. 1). The DNA binding domain has been particularly well conserved among vertebrates—the minimal DNA binding domain contains a stretch of 131 amino acids that is identical in the c-Myb proteins from chickens, mice, and humans.

The v-Myb protein encoded by avian myeloblastosis virus (AMV) is an activated allele of c-Myb, truncated at both ends and containing a number of point mutations that alter the protein sequence and contribute to its transforming activity [42]. Unlike v-Myb, the normal c-Myb protein has only weak transforming activity, suggesting that the protein is under strict negative regulation and that mutations are required to unmask its transforming potential [12,13,43–46].

Besides c-Myb, vertebrates also express two closely related transcription factors, A-Myb and B-Myb. The three Myb proteins have nearly identical DNA binding domains and similar overall structures (Fig. 2). The A-Myb protein is expressed in a subset of the cells that express c-Myb, including lymphoid cells and epithelial tissues [47,48]. Mice lacking functional A-Myb genes have defects in spermatogenesis and mammary gland development [49] and ectopic expression of A-Myb causes follicular hyperplasia in mice [50]. In contrast, the B-Myb protein is expressed in all replicating cells and is required for transition through the cell cycle [51]. Despite the fact that they have different expression patterns and functions in vivo, all three Myb proteins have indistinguishable DNA binding activities and are capable of activating the same promoters in transfection assays [47,52,53].

Identification of Myb regulated genes

The Myb proteins have been shown to bind to and regulate the promoters of a number of vertebrate genes [1]. The best characterized of these is the chicken mim-1 gene, whose promoter contains three Myb binding sites [54] and is activated by a combination of c-Myb plus C/EBPbeta in immature myeloid cells [55]. Although both c-Myb and v-Myb are able to bind the mim-1 promoter and to activate mim-1 promoter-reporter gene fusion constructs in transfection experiments [54], only c-Myb is able to activate the endogenous, chromatin-embedded mim-1 gene. In contrast, only v-Myb is able to activate the GBX2 gene, which encodes a homeodomain transcription factor in v-Myb-transformed cells [56]. This suggests that the mutations in v-Myb that render it oncogenic also alter its specificity for regulating specific genes.

A number of Myb-regulated genes have also been identified in mammalian cells [1]. Most prominent among these are c-myc [57,58], Bcl-2 [59,60], c-kit [61,62], CD34 [63,64], and the T-cell receptor delta [65,66], all of which play important roles in the differentiation, proliferation, survival, or function of hematopoietic cells. Despite this success, it is not possible to explain, based on the identities of the known Myb-regulated genes, how the v-Myb protein is able to transform immature myeloid cells or how c-Myb is able to control the differentiation and/or proliferation of immature hematopoietic cells.

Combinatorial regulation of Myb target genes

On a number of Myb-regulated promoters, the Myb protein binding sites are located immediately adjacent to binding sites for other transcription factors, such as C/EBP proteins [55,67,68], PU.1 [68], Ets-1 [69,70], or CBF [66,71]. In each case, Myb proteins cooperate with the other transcription factors to cooperatively activate the promoter. Ectopic expression of Myb plus C/EBP-β leads to activation of the myeloid cell-specific mim-1 gene, even in nonhematopoietic cells that usually never express mim-1 [55]. This has led to a model in which the combinatorial actions of two or more transcription factors with overlapping expression patterns could result in tissue-specific gene regulation [55,72].

Alterations in Myb proteins change their specificities

The Myb transcription factors have DNA binding and central transcriptional activation domains that resemble similar functional domains from other proteins [1]. Indeed,

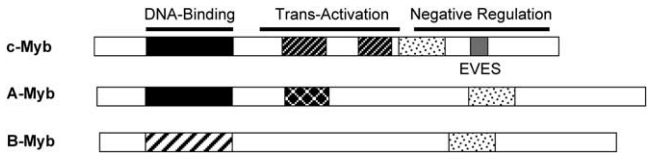

Fig. 2. Myb protein structures. The three vertebrate Myb proteins have nearly identical DNA-binding domains near the N-terminus, but diverge elsewhere. The c-Myb and A-Myb proteins have some sequence identity in the transactivation domain, and all three proteins have a weakly conserved domain (stippled) near the C-terminus.

fusion proteins comprised of the c-Myb or v-Myb DNA binding domains fused to heterologous transcriptional activation domains retain the ability to activate plasmid-based reporter genes [73–76]. However, substitution of the native transcriptional activation domain with a heterologous one from VP16 changed the biological activity of v-Myb [77], and detailed mutagenesis studies identified conserved elements in the transcriptional activation domain of v-Myb that are required for transformation but not for activation of plasmid-based reporter genes [78]. Fusions between the v-Myb or c-Myb DNA-binding domain and the hormone-binding domain of the estrogen receptor, which contains its own transcriptional activation domain, generated an estrogen-regulated hybrid that activated plasmid-based reporter genes in a hormone-dependent manner [33,79]. These Myb-ER fusions have been used to identify Myb-regulated genes [79,80]. However, the Myb-ER fusion proteins had altered biological activities, and the v-Myb-ER fusions lacked the ability to transform cells, suggesting that the fusion proteins had lost the most biologically relevant functions of the Myb proteins [33,79]. These results show that results from plasmid-based reporter genes do not necessarily correlate with the biological activities of Myb proteins. They also suggest that changes in the structure of Myb proteins, such as replacing the native transcriptional activation domain with regulatory domains from hormone receptors, results in loss of the most important biological activities of the Myb protein.

Myb proteins are subject to numerous posttranslational modifications

Myb transcription factors have been shown to be modified by numerous posttranslational modifications, including reduction and oxidation [81–84], phosphorylation [85–89], acetylation [90,91], and sumoylation [92,93]. Many of these modifications are affected or eliminated by the mutations and deletions that distinguish v-Myb, suggesting that elimination of the modifications contributes to the transforming activity of the oncogene and is a crucial difference between c-Myb and v-Myb. Because of their absence in v-Myb, all of the known modifications of c-Myb have been postulated to contribute to its negative regulation. However, there is no explanation for why so many changes in posttranslational modification should be required to convert c-Myb to an oncogene. In addition, there have been no tests of whether the modifications affect some other feature of c-Myb, such as the ability to activate specific genes.

Context-specific functions of Myb proteins

Two types of results reflect the dramatic context-specific activities of Myb transcription factors. First, all of the Myb-regulated genes identified to date are expressed in tissue-specific patterns and are expressed only in a subset of the cells that express Myb proteins. For example, the chicken *mim-1* gene is induced by c-Myb in immature granulocytes and eosinophils, but not in other hematopoietic cells, such as erythroblasts or lymphoid cells, that express even higher levels of c-Myb [54,55]. Similarly, Myb proteins are important regulators of the Bcl-2 gene in immature myeloid cells and in colon epithelial cells, but not in other cell types [37,80,94], and the c-kit gene is induced by c-Myb only in immature myeloid cells [61,80]. These results suggest that combinatorial interactions with other transcription factors, cofactors, or accessory proteins influence Myb specificity and the genes that are regulated in each cell type [55,72].

Table 1
Myb protein activities

Myb protein	Reporter gene	Endogenous gene
A-Myb	+++	−
B-Myb	+	−
c-Myb	++	+++
v-Myb	++	−

Note. All Myb proteins activate the same reporter genes. Only c-Myb activates the endogenous mim-1 gene.

An additional type of context specificity is reflected by differences between plasmid-based reporter assays and the regulation of endogenous chromosomal genes. As mentioned above, the A-Myb, B-Myb, c-Myb, and v-Myb proteins can all bind the same sites in DNA, and all can activate reporter genes containing the promoter from the chicken *mim-1* gene [52,54,95–97]. However, as summarized in Table 1, only c-Myb can activate expression of the endogenous *mim-1* gene in chicken cells [54, 98], suggesting that plasmid-based reporter gene assays fail to distinguish the important biologically relevant differences between different Myb proteins.

Results and Discussion

In recent years, our laboratory has focused on the regulation of the c-Myb protein, with an emphasis on understanding *how* signaling pathways and protein interactions regulate its activity [87,95,99–101]. However, it has become increasingly clear that the specificities of Myb proteins change in different cell contexts and that important differences in Myb activity (e.g., the differences between v-Myb and c-Myb regulating the *mim-1* gene) are not adequately reflected by commonly used plasmid-based reporter gene assays. To address these issues, we have developed improved tools, such as microarray-based gene expression assays that follow the expression of endogenous, chromatin embedded genes, and virus-based expression systems that express wild-type and mutant Myb proteins with high efficiency in a variety of cell types. These tools allow us to begin studying the biologically relevant activities of Myb proteins in human cells.

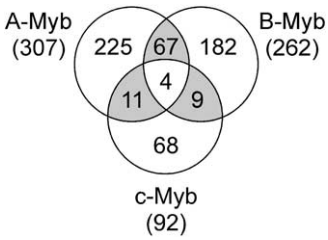

Fig. 3. Activities of A-Myb, B-Myb, and c-Myb. The Venn diagram summarizes the results of gene activation assays performed using Affymetrix U95A-E GeneChips, with MCF7 cells infected by adenoviruses expressing A-Myb, B-Myb, or c-Myb. See text for details.

Different activities for A-Myb, B-Myb, and c-Myb

Vertebrates express three related Myb transcription factors, A-Myb, B-Myb, and c-Myb, all of which are expressed in immature, proliferating hematopoietic cells and leukemias. All three proteins have DNA-binding domains that are nearly identical, all bind the same DNA sequence in vitro, and all activate the same reporter gene constructs in transient transfection assays, suggesting that all should have similar activities on endogenous genes. However, mouse knockouts have shown that the three proteins have distinct biological functions. To address the discrepancies between in vivo functional differences and the apparently indistinguishable transcriptional activities of the three Myb proteins, we generated recombinant adenovirus vectors expressing each transcription factor and then used the viruses to ectopically express A-Myb, B-Myb, or c-Myb in human tissue culture cells. After 16 h, RNA was prepared and analyzed using Affymetrix GeneChip microarrays to assess changes in endogenous gene expression. Since these results were recently published [96], they are only summarized here.

The main result from the microarray assays of cells infected with adenoviruses expressing different Myb proteins is that each version of Myb had a completely different activity and led to the activation of a different set of endogenous genes. The results are summarized in Fig. 3, showing a Venn diagram analysis of the genes that were activated following expression of each Myb protein. This analysis was performed with the Affymetrix U95A-E set of GeneChips, with probes representing more than 65,000 known and hypothetical genes and EST clones. More than 300 genes were activated or repressed more than twofold following expression of one or more of the Myb proteins. However, very few genes were activated in response to more than one Myb protein. For example, A-Myb expression led to the activation of 307 genes, of which only 67 were also activated in response to B-Myb and only 11 were also activated in response to c-Myb. Remarkably, of more than 65,000 genes represented on the arrays, only 4 genes were activated in response to all three Myb proteins [96].

The results shown in Fig. 3 are not unexpected, given the fact that each Myb protein has a distinct biological activity. On the other hand, all three proteins bind the same DNA sequence and activate the same reporter gene constructs in transfection assays [52,57,96,102,103], suggesting that they should have been able to activate the same endogenous genes when expressed ectopically in human cells. Thus, these results lead to several important conclusions. First, they show that the results from reporter gene assays can be misleading, since they fail to distinguish differences in Myb protein activities that are reflected by the biology and by the microarray assays. Thus, it is necessary to use biological or microarray assays to accurately compare the activities of different Myb proteins. Second, the results show that, despite being ectopically overexpressed from an adenovirus vector, each Myb protein interacted differently with the cellular milieu, including the available cofactors and cooperating transcription factors, in order to induce a specific set of gene expression changes. This means that unique features, such as differences in the transcriptional activation domains, determine the activity and specificity of each protein. The nearly identical DNA binding domains played a less important role in determining which endogenous genes became activated.

Cell type-specific changes in Myb protein activities

To address the tissue specificity of Myb protein activity, we have repeated the microarray experiment described above in other cell types. In each case, we obtained results similar to those shown in Fig. 3: ectopic expression of A-Myb, B-Myb, or c-Myb led to the activation of unique sets of genes. However, the identities of the genes were cell type specific (W. Lei and S.A. Ness, submitted for publication). To illustrate this point, the Venn diagram in Fig. 4 compares the genes from three different cell types that, like the genes shown in Fig. 3, were expressed above a minimum threshold and were induced at least 2.5-fold as a result of A-Myb, B-Myb, or c-Myb protein expression. The comparison shows that the induced genes were almost completely cell type specific. Thus, only 1 of the 126 genes analyzed from MCF7 cells were also induced in lung epithelial cells, and only 19 were also induced in lung fibroblasts. There were no genes induced in all three cell types.

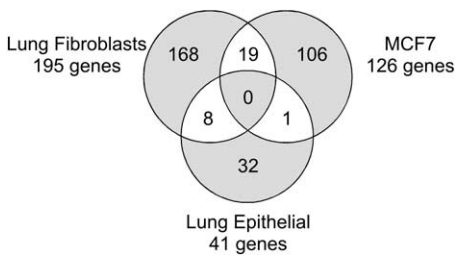

Fig. 4. Venn diagram. Comparison of Myb-induced genes from MCF7, primary lung epithelial cells or primary lung fibroblasts. In each case, only the genes that were expressed above a threshold of 1000 Affymetrix units and induced at least 2.5-fold by one of the Myb proteins were included. Microarray assays were performed using Affymetrix U95A GeneChips.

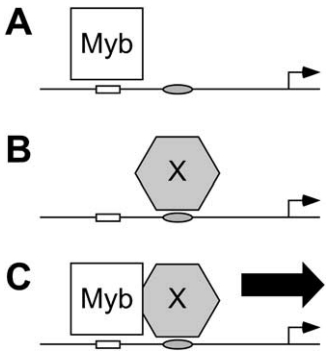

Fig. 5. Combinatorial regulation. The gene is not expressed when (A) only Myb or (B) only another factor "X" are expressed. Activation of the promoter requires that both Myb and "X" are coexpressed (C). This model explains tissue-specific regulation if Myb and factor "X" have overlapping patterns of expression.

These results lead to several important conclusions. First, even ectopic expression of the Myb proteins from adenovirus vectors was unable to overcome the cell-type-specific regulatory mechanisms that affected the Myb proteins. In other words, the Myb transcription factors regulated different genes in different cell types, so they must have interacted or cooperated with cell-type-specific cofactors or accessory proteins in those cells that determined their specificity. Second, these results are in stark contrast to the results obtained with plasmid-based reporter genes that can be activated by Myb proteins in many cell types [54,95,96,101].

Model 1: Cooperating factors come and go, but Myb proteins stay the same

One model to explain the context-specific effects is that to regulate specific genes Myb proteins must cooperate with other transcription factors, bound to adjacent binding sites on promoters, that are themselves regulated or expressed in a tissue-specific manner (Fig. 5). Myb-binding sites are frequently located adjacent to the binding sites for other transcription factors in promoters. For example, in the chicken mim-1 promoter, the high-affinity Myb-binding site is positioned next to a binding site for NF-M, the avian form of C/EBP-β [54,55]. A similar arrangement is found in the murine neutrophil elastase promoter [68]. Activation of these two promoters requires coexpression of Myb and C/EBP-β. Indeed, ectopic expression of c-Myb plus C/EBP-β can activate the endogenous mim-1 gene in transfected fibroblasts, even though mim-1 is normally not expressed in such cells [55]. In this model of combinatorial regulation, Myb and C/EBP-β each interact with the promoter and with separate components of the transcription machinery. The transcriptional activation domain of c-Myb has been shown to interact with CBP, a transcriptional coactivator with histone acetyltransferase activity [104–107]. This interaction is even conserved in *Drosophila* Myb [108], suggesting that it is crucial to the function of c-Myb. C/EBP-β on the other hand, interacts with components of the SWI/SNF complex [109], and fusing the SWI/SNF interaction domain from C/EBP-β onto c-Myb generates an activated Myb that no longer requires C/EBP-β for activation of the mim-1 gene [109]. This suggests that the sole function of C/EBP-β is to donate the SWI/SNF interaction function, which when coupled with the CBP interacting function of c-Myb, is sufficient to activate the endogenous mim-1 gene. Thus, the combinatorial effects of c-Myb plus NF-M appear to be sufficient to explain the regulation of the mim-1 and neutrophil elastase promoters.

However, some types of data are difficult to explain with the simple combinatorial model outlined above. For example, A-Myb and B-Myb also interact with CBP [110,111], and they can bind to and activate the mim-1 promoter in vitro and in reporter gene transfection assays, but they are unable to cooperate with C/EBP-β to activate the endogenous mim-1 gene. Thus, some feature in addition to CBP interaction must be required for activation of specific genes by c-Myb. This model also fails to account for the many different and highly regulated modifications that occur on the c-Myb protein or to explain how the mutations in v-Myb endow it with such a qualitatively distinct gene expression activity. In the combinatorial model, all transactivation domains are equivalent, so it is difficult to explain subtle differences in transcription factor activities.

Model 2: A context-specific modification code

A second possibility is that the Myb protein activities change when they are introduced into different cellular environments, perhaps due to differences in posttranslational modifications. The c-Myb protein is most highly expressed in immature hematopoietic and epithelial cells that are rapidly proliferating, but that can differentiate in response to extracellular signals such as cytokine stimulation or cell–cell contacts [1]. The v-Myb oncoprotein blocks the differentiation of immature hematopoietic cells, suggesting that Myb proteins regulate differentiation. However, Myb proteins also influence apoptosis by regulating the expression of important genes such as Bcl-2 [37,60,94], and most of the known Myb-regulated target genes are encoded in mature differentiated cells, not the immature, proliferating progenitors [1]. Thus, Myb proteins are apparently involved both in keeping cells immature and proliferating and also in promoting terminal differentiation. These two contradictory activities suggest that c-Myb may have alternate activities, such as the ability to regulate different sets of genes in different circumstances, and that the switch regulating these activities is subject to extracellular signals.

An expanded model to explain the different activities of Myb proteins is centered on the fact that Myb proteins are subject to a wide range of posttranslational modifications that could alter their ability to regulate specific genes, perhaps by controlling interactions with other transcription

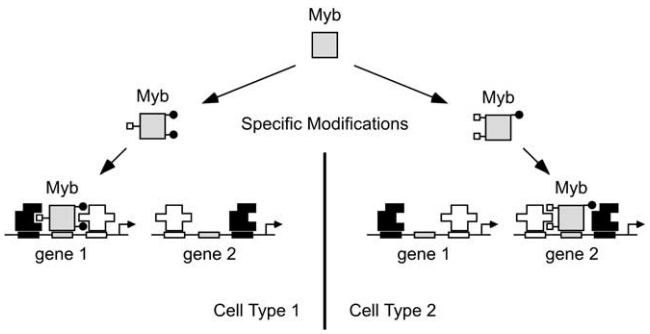

Fig. 6. A Modification code model of Myb specificity. When Myb proteins are introduced into two different cellular environments, they may become decorated with different sets of posttranslational modifications, permitting them to interact and cooperate with distinct sets of other transcription factors, leading to the activation of different sets of genes. Changes in modifications caused by activated signaling pathways would also lead to changes in Myb activity and choices between proliferation and differentiation.

factors or components of the transcriptional machinery. In this view, each cellular environment has a different combination of modification activities, such as activated protein kinases or phosphatases, protein acetylases, oxidation–reduction pathways or ubiquitin or sumo ligases. Thus, the c-Myb protein expressed in two different cellular environments would become decorated with a unique and specific set of modifications or "code" that determined its ability to regulate specific sets of genes (Fig. 6). Since many of the relevant modification enzymes are known to be downstream of signaling pathways, this model provides a mechanism to explain how activated signaling pathways, for example, in response to cytokine stimulation, could affect the specificity of Myb proteins and the consequent expression of differentiation- or proliferation-specific genes. This model is attractive because it proposes a purpose for the many and varied posttranslational modifications that have been detected on Myb proteins, as a modification code that controls transcriptional activity.

These models are not necessarily exclusive, but they each have important implications for understanding how genes are regulated in cell-type-specific context and how mutations affect the activity of transcription factors. Both of the models for context specificity imply that the cellular environment is subject to change, for example, through the processes of differentiation or oncogene-induced transformation. Thus, whereas c-Myb expression is required to keep immature hematopoietic cells proliferating [34,112], most of the Myb-regulated genes that have been identified are expressed in terminally differentiated, nonproliferating cells [1], suggesting that c-Myb plays a role both in stimulating proliferation and also in promoting terminal differentiation. These apparently contradictory roles are consistent with the idea that c-Myb has alternate activities and is able to affect the regulation of different sets of genes in different circumstances and in response to extracellular signals. To distinguish between these models, it will be necessary to determine whether Myb proteins acquire different posttranslational modifications in different cell types and whether such modifications affect the specificity of Myb proteins regulating chromosome-embedded genes.

Acknowledgments

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