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MYB – A regulatory factor in hematopoiesis

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Abstract

MYB is a transcription factor which was identified in birds as a viral oncogene (v-MYB). Its cellular counterpart was subsequently isolated as c-MYB which has three functional domains - DNA binding domain, transactivation domain and negative regulatory domain. c-MYB is essential for survival, and deletion of both alleles of the gene results in embryonic death. It is highly expressed in hematopoietic cells, thymus and neural tissue, and required for T and B lymphocyte development and erythroid maturation. Additionally, aberrant *MYB* expression has been found in numerous solid cancer cells and human leukemia. Recent studies have also implicated *c-MYB* in the regulation of expression of fetal hemoglobin which is highly beneficial to the β-hemoglobinopathies (beta thalassemia and sickle cell disease). These findings suggest that *MYB* could be a potential therapeutic target in leukemia, and possibly also a target for therapeutic increase of fetal hemoglobin in the β-hemoglobinopathies.

Keywords

Hematopoiesis; Erythropoiesis; Fetal hemoglobin; C-MYB; Transcription factor

1. Introduction

v-MYB is an oncogene from avian myeloblastosis virus (AMV) (Hall et al., 1941) and E26 (another avian virus), implicated to be one of the oncogenes that cause myelomas and lymphomas in birds (Radke et al., 1982; Moscovici et al., 1983; Lipsick and Wang, 1999). *c-MYB* (*MYB*) was subsequently identified as a cellular homologue of the virus *v-MYB* (Klempnauer et al., 1982; Boyle et al., 1983; Klempnauer et al., 1983; Gonda et al., 1985; Majello et al., 1986) (Table 1). Other forms of *MYB*, *A-MYB* and *B-MYB*, exist in humans encoding transcription factors A-MYB and B-MYB, respectively, that share some homology, including the DNA binding domain, with c-MYB (Ganter and Lipsick, 1999; Bergholtz et al., 2001).

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Conflicts of interest

None declared for all authors.

In this review *MYB* is used interchangeably with c-*MYB* and the encoded transcription factor referred to, as MYB. Since its discovery in the 1980s, MYB has been recognized as a crucial transcription factor in hematopoiesis and erythropoiesis. *MYB* is tightly regulated, deregulation of *MYB* is oncogenic; it has been shown to undergo rearrangement or translocation, leading to aberrant expression in human leukemias and lymphomas (Stenman et al., 2010; Pattabiraman and Gonda, 2013). *MYB* has also been shown to be highly expressed in colorectal, breast and pancreatic cancers (Biroccio et al., 2001; Persson et al., 2009). MYB has a critical physiological role in normal hematopoiesis; it is essential for definitive red cell maturation and its expression is precisely controlled during the different stages of hematopoiesis (Mucenski et al., 1991). More recently, studies have revealed that *MYB* has a role in regulating fetal hemoglobin gene expression (Jiang et al., 2006; Thein et al., 2007; Stadhouders et al., 2014), a major modifier of the severity of the beta hemoglobinopathies - beta thalassemia and sickle cell disease (Gardner and Thein, 2016; Thein, 2018).

While much has been learnt about *MYB* (see reviews, Ramsay and Gonda, 2008; Pattabiraman and Gonda, 2013; George and Ness, 2014; Paikari and Sheehan, 2018), a lot remains to be resolved about the regulatory control of *MYB* expression and how it impacts its function. *MYB* is considered as an oncogene, but the mechanism underlying this process is not clear. In some cancer cells, *MYB* expression is relatively higher, but it is not clear if the elevated expression is the cause of the oncogenic process. Forced over-expression of *c-MYB* did not cause the cells to become cancerous. Further, the key targeted gene(s) promoting oncogenesis regulated by MYB are still unknown, although many genes regulated by MYB have been investigated during differentiation, proliferation, apoptosis and development. While v-MYB and c-MYB have been studied for > 3 decades, the structure of the whole protein is not known. Although functional dissection of MYB has revealed three domains - DNA binding domain (DBD), transcription activation domain (TAD), and negative regulatory domain (NRD)- (Fig. 1), the functional roles of these domains, especially TAD and NRD, have yet to be fully determined. For instance, it is not clear if the NRD is required for all of its role in oncogenesis, apoptosis, proliferation and differentiation. Notably, v-MYB lacks NRD in the C-terminus, which is not surprising that it functions as a transcriptional activator all the time, a property that likely contributes to its role in leukemogenesis.

Regulation of *MYB* expression is complex involving several levels, via its proximal promoter region (Sullivan et al., 1997) and microRNAs (miRNAs) at the posttranscriptional level (Lu et al., 2008; Zhao et al., 2009; Sankaran et al., 2011). Enforced miR-15a expression blocked both erythroid and myeloid colony formation in vitro, suggesting an important autoregulatory c-MYB-miR-15a circuit in human hematopoiesis (Zhao et al., 2009). A delayed HbF to HbA switch, along with persistently elevated HbF levels, in infants with trisomy 13 (Huehns et al., 1964) prompted further experiments that support involvement of miRNAs 15a and 16–1 in regulation of *MYB* expression. The gene encoding miRNAs 15a and 16–1 is localized on chromosome 13q14 that was unambiguously associated with the increased HbF trait in these infants (Sankaran et al., 2011). Recent experiments show that *MYB* is additionally controlled distally by enhancer elements > 80 kb

upstream of its promoter (Stadhouders et al., 2014) and mouse studies show that the activity of *Myb* takes place within an active chromatin hub (Stadhouders et al., 2012).

2. *MYB* proteins and its transcripts

c-MYB is a transcription factor which is vital for survival. It is predominantly expressed in immature hematopoietic cells, and its expression remains precisely controlled throughout development. Knockout of the gene results in lethality at day 14 of embryogenic stage in mouse (Mucenski et al., 1991; Vegiopoulos et al., 2006).

As for other transcription factors, MYB proteins are able to bind DNA. The consensus sequence for DNA binding is 5′-YAACG/TG -3 (Howe and Watson, 1991); (Bergholtz et al., 2001), variation in the last 2 nucleotides of the consensus results in lower DNA binding. The MYB DNA binding domain is located at the N-terminal of the MYB protein. This region is also called SANT-like domain. A SANT domain is a protein domain that allows many chromatin remodeling proteins to interact with histones. SANT is an acronym for “Swi3, Ada2, N-Cor, and TFIIIB”. The SANT domain is highly conserved, and is similar to MYB DNA-binding domains. Although the structure for the DNA binding domain and the DNA binding form in solution has been solved (Ogata et al., 1995; Ogata et al., 1996; Tahirov et al., 2001) the structure of the whole protein is still not known.

It is interesting that MYB proteins have a unique DNA binding motif and lately, this motif has been found to be conserved among vertebrates and higher plants (Ambawat et al., 2013). The motif consists of imperfect repeats of about 50 amino acids. The conserved tryptophan is spaced between 18/19 amino acids and it participates in hydrophobic core formation. Each DNA binding domain consists of a structure of helix-turn-helix revealed by NMR (Ogata et al., 1992; Ogata et al., 1994; Ogata et al., 1995). Avian, mouse and human c-MYB has 3 DNA binding motives, while v-MYB from avian and E26 viruses has only two DNA binding motives (Fig. 1). The comparison between animal and v-MYB prompted the suggestion that the first DNA binding domain in animal MYB is not necessary for the DNA binding. Indeed, DNA binding assays confirmed that intact second and third DNA binding domains alone are able to bind DNA (Klempnauer and Sippel, 1987), and likely to contain the core DNA binding domains. All the MYB proteins, v-MYB from AMV and E26 virus, and animal c-MYB, are located in the nucleus and are able to bind the same DNA sequence. Although the first DNA binding domain in c-MYB is not required for DNA binding, it does facilitate its DNA binding, in that it mediates the interaction of other parts of the MYB protein and its associated proteins. Point mutation in this DBD of MYB changed the DNA-binding properties at a physiological target gene (Ivanova et al., 2007).

siRNA knockdown and global expression profiling in combination with chromatin immunoprecipitation (ChIP) assays, identified a set of c-MYB target genes in K562, an human erythroid cell line (Lorenzo et al., 2011). The genes included *MYADM, LMO2, GATA2*, *STAT5A*, and *IKZF1*. ChIP followed by high-throughput DNA sequencing (ChIPseq) relies on good antibodies, and currently available MYB antibodies interfere with ChIP assays. Bengtsen et al. (Bengtsen et al., 2015) used Digital Genomic Footprinting (DGF) to obtain a global picture of c-MYB occupancy in the human genome, the results

showed that the predicted c-MYB specific binding sites vary strongly among hematopoietic cell types, but that a set of c-MYB footprints are common to all cell types analyzed.

The nuclear localization sequence of MYB has yet to be further confirmed. By sequential deletion experiments, Sakura et al. (Sakura et al., 1989) found that MYB protein lacking the first 2 DNA binding motives remained in the nucleus. This construct lacks transcription activation activity since it lacks DNA binding domain. Protein without the transactivation domain remained in the nuclei, while the construct with all three DNA binding motifs was found partially in the nuclei. These results suggest that the nuclear target sequence is dispersed over the N-terminal region and that the DNA binding domain has multiple functions. It can bind DNA, contains the nuclear localization signal, and is also involved in intramolecular interaction with other factors. Interestingly, Bengtsen et al. (Bengtsen et al., 2015) showed that MYB DNA binding was dynamic and varied among different hematopoietic cell types.

2.1. MYB trans-activation

The MYB transcriptional activation domain (TAD) is located in the middle of the protein (Fig. 1). By constructing vectors containing different part of c-MYB, Sakura et al. showed that the TAD domain was located in amino acids 241 to 325, although Kalkbrenner et al. (Kalkbrenner et al., 1990) defined the transactivation domain within MYB amino acids 275 to 327 by fusing the human c-MYB C-terminal regions to GAL4 DNA binding domain. Homologous comparison between v-MYB and its cellular counterpart revealed that v-MYB lacks the first 71 amino acids and 197 amino acids at C-terminus (Fig. 1). Since both v-MYB and c-MYB function as transcription factors, this suggests that the C-terminus in c-MYB is not required for transactivation. The dimerization domain is inferred from the different fusions, and may be located to amino acid 201 to 275, possibly up to 327 (Kalkbrenner et al., 1990). Nomura et al. reported that c-MYB can dimerize through its leucine zipper domain in the middle of the protein. c-MYB with mutated leucine zipper could not form dimers and interrupted transactivation of the wild type MYB protein (Nomura et al., 1993).

c-MYB plays a critical role in transactivation in hematopoietic cells and tissues, this role is mediated by interaction of TAD with CBP (CREB binding protein) and p300. LxxLL-motif is a highly conserved region on c-MYB interacting with p300, the partner domain on CBP/p300 is the KIX domain (Kasper et al., 2013). While the interaction between MYB TAD and CBP/p300 is required for its transcriptional regulation, this interaction could also directly repress target gene expression (Zhao et al., 2011). Apart from CBP and p300, MYB is able to interact with > 50 proteins in mice and human (Chatr-Aryamontri et al., 2017); (http://thebiogrid.org, Fig. 2).

Mutational studies of a region called FAETL domain (amino acid 296 to 371) of v-MYB showed that it is required for transcriptional activation and transformation of primary chicken myelomonocytic cells. Fu and Lipsick (Fu and Lipsick, 1996) showed that deletion of this region (amino acid 321–330) results in nonfunctional protein. Notably, they suggested that the leucines in this leucine rich region are not required for its function.

However, alignment between v-MYB and c-MYB, A-MYB from different species revealed high conservation (Ganter and Lipsick, 1999).

EVES is another important motif at the C-terminus of MYB. This motif is highly conserved in vertebrate c-MYB and contains a known site for phosphorylation which has previously been implicated in the negative regulation of c-MYB. Dash et al. (Dash et al., 1996) demonstrated that c-MYB interacts through this motif with p100, a ubiquitously expressed transcriptional coactivator. In addition, the EVES motif also mediated intramolecular regulation of c-MYB by interacting with the N-terminus region (Dash et al., 1996). This interaction with p100 implicates its role in the expression of c-MYB, cell proliferation and differentiation. Since the intramolecular interaction influences the intermolecular interaction, this domain is named the negative regulatory domain.

Stability of transcription factors is another key factor for its transactivation role. Bies et al. (Bies and Wolff, 1997; Bies et al., 1999) found that c-MYB truncated 248 amino acids from the C-terminus has a fourfold increased half-life because of its ability to escape rapid degradation by the ubiquitin-26S proteasome pathway. What is clear is that the PEST (proline, glutamic acid, serine, threonine-rich region) region is not required for its stability but 87 amino acids at its C-terminus are essential. Kanei-Ishii et al. (Kanei-Ishii et al., 2004a; Kanei-Ishii et al., 2004b; Kanei-Ishii et al., 2008) reported that multiple targeted sites have been found at c-MYB C-terminus; Fbxw7 functions as an ubiquitin ligase targeting c-MYB through NLK (Nemo-like kinase)-induced degradation.

2.2. MYB transcripts

Dudek and Reddy first reported the existence of 2 isoforms of c-MYB proteins (Dudek and Reddy, 1989), both forms being present in normal and tumor cells. Since then, many isoforms of c-MYB have been found (Fig. 3). The major 2 isoforms in human are 89 kD (isoform 1) and 72 kD (isoform 2) in size. The p89-MYB has one extra spliced exon 9B (originally named 9A) which encoded 121 amino acids (Fig. 3). The dominant human MYB isoform (p72, isoform 2) is 72 kD (640 amino acids) (Fig. 3). Some publications reported that p89-MYB is more active in chickens (Woo et al., 1998) and in humans (O'Rourke and Ness, 2008). However, Baker et al. (Baker et al., 2010) demonstrated that the p89-MYB isoform is not required for hematopoietic development. The study generated a null-mutant mouse where exon 9B has been systemically deleted resulting in the absence of the p89-myb transcript and protein. Loss of the p89- encoding isoform does not have any deleterious effects on mammalian hematopoiesis and development. Given that the p89 isoform is a minor species in most published results and in our detection in HUDEP-2 and K562 erythroid cells (unpublished data), it would easy to conclude that p89 does not play a major role in hematopoiesis and development.

By comparing different platforms of RNA-seq, analysis of MYB alternative splicing detected at least 29 different transcript isoforms in human CD34+ progenitor and Jurkat-T cells (Brown et al., 2017). The functions of these minor isoforms in cell proliferation and differentiation are not very clear.

3. *MYB* is an oncogene and it regulates cell proliferation and differentiation

Being a cellular counterpart of v-MYB, c-MYB has been labeled an oncogene. c-MYB is a common integration site for avian and murine retroviruses, leading to a variety of leukemias (Oh and Reddy, 1999; Ramsay and Gonda, 2008; Zhang et al., 2012). Further studies indicated that c-MYB may be associated with some epithelial cancers and even some neural carcinomas where c-MYB expression is relatively higher in the malignant cells. However, overexpression of full length c-MYB in animal cells do not appear to be oncogenic (Grasser et al., 1991). Investigations showed that persistent expression of c-MYB blocks cellular differentiation. At present, the proposed mechanisms of MYB oncogenesis are: 1. overexpression; 2. Translocation leading to fusion with other genes, resulting in a hybrid protein which change the interaction with other proteins; 3. mutation in TAL-1 promoter creating a super MYB binding site in some leukemia (Emambokus et al., 2003; Carpinelli et al., 2004; Sandberg et al., 2005; Malaterre et al., 2008; Mansour et al., 2014).

Early studies revealed that c-MYB plays a critical role in stem cell proliferation and differentiation (Gewirtz and Calabretta, 1988; Mucenski et al., 1991; Orlic et al., 1995). Knockdown of c-MYB in human bone marrow cells with antisense oligonucleotides results in decreased colony formation in both size and number (Gewirtz and Calabretta, 1988), while *c-Myb* knockout in mouse is lethal due to the impaired red cell development (Mucenski et al., 1991). A mutation, M303 V in *Myb*, blocked the T, B and red cell development with a remarkable increase in numbers of hematopoietic cells (Sandberg et al., 2005). The mutation resulted in the disruption between c-Myb and p300, further validating that the transactivation domain of c-MYB is encompassed within amino acids 275 to 327. It is interesting that amino acid M303 is next to the transactivation motif LxxLL (amino acid 298–302) which suggests that even one key residue change at that region could disrupt or alter its function.

c-MYB expression is precisely controlled during differentiation and proliferation; a conditional decrease promoted differentiation (Hogg et al., 1997; White and Weston, 2000), while forced expression of c-MYB inhibited cell differentiation in myeloid and erythroid cell lines (McMahon et al., 1988; Selvakumaran et al., 1992). Studies with v-myb showed that even a single amino acid change in the DNA binding domain would lead to different cell fates suggesting that different forms of MYB regulate different sets of differentiation-specific genes, leading to alternative directions of differentiation (Introna et al., 1990).

c-MYB is a stem cell regulator in multiple tissue compartments, including hematopoietic stem cells (HSC), neurons and vascular smooth muscle cells (Ramsay, 2005; Sandberg et al., 2005; Sakamoto et al., 2006; Malaterre et al., 2007; Malaterre et al., 2008; Lieu and Reddy, 2009; Shikatani et al., 2016), although most studies address its regulatory effects on hematopoietic stem cells. It is known that pluripotent stem cells express more c-MYB than relatively differentiated cells. One of the conventional transforming transcription factors for iPS cells is c-MYC which is a c-MYB target gene (Nakagoshi et al., 1992; Cogswell et al., 1993). Evidence that c-MYB binds to c-MYC promoter has been provided either by ChIP assays or by whole genome ChIP-seq (Berge et al., 2007; Ciznadija et al., 2009; Quintana

et al., 2011a; Quintana et al., 2011b). However, the role of c-MYB regulating *c-MYC* is complicated by the fact that, while c-MYB can regulate *c-MYC* expression, it is not essential for this function. It is interesting that c-MYB also binds to KLF4 promoter, another iPS cell transformation factor (Quintana et al., 2011a). c-MYB also bound to NANOG promoter, and while NANOG cannot initiate the iPS cells reprogramming, it is required for the acquisition of pluripotency, implicating the role of c-MYB in reprogramming.

MYB also appears to have a role in cell cycling via its interaction with cyclins. Cyclin-dependent kinases (CDKs) are the catalytic subunits of a family of mammalian heterodimeric serine/threonine kinases in the control of cell-cycle progression, transcription and neuronal function (Malumbres and Barbacid, 2005). c-MYB has been shown to interact with cyclin D1 and D2 (Ganter et al., 1998; Lei et al., 2005). v-MYB and c-MYB appears to interact differently with the D-type cyclins; v-MYB could be inhibited by D-type cyclins, but not c-MYB (Ganter et al., 1998).

Accumulated evidence showed that c-MYB interacts with other cell cycle factors and plays a role in G2/M transition in cell cycle (Frampton et al., 1996); (Wasner et al., 2003; Nakata et al., 2007). c-MYB bound to the promoters of cyclin B1 and E1, and cyclin E1 expression seems to be c-MYB-dependent (Malaterre et al., 2007; Nakata et al., 2007). All these observations suggest that c-MYB is functional in multiple steps of the cell cycle, both in G1 and G2 phases.

Genome-wide binding studies showed that c-MYB bound > 10,000 promoters (Quintana et al., 2011a; Quintana et al., 2011b), many of which belong to cell cycle regulators, such as cyclin B1, CXCL4, KLF4. Studies of the c-MYB binding profile in human CD34+ cells and human Jurkat T cells, showed that c-MYB binding to gene promoters is highly dynamic during cell cycle. The specificity of c-MYB binding is not only dramatically different in small subpopulations of cells, but MYB also actively repositions itself in sub-sets of cells (Quintana et al., 2011b). For example, c-MYB associated with the promoter of the Cyclin E1 gene only in G2/M phase cells, while the protein was expressed at equal levels in the different cell cycle fractions. Given the DNA promoter sequence and DNA binding domain of c-MYB would not change during the cell cycle, it was suggested that the mechanism may derive from the protein interaction between c-MYB and other factors (Quintana et al., 2011b). It is this dynamic binding that leads to the different sets of gene expression by c-MYB during different phases of cell cycle.

3.1. Aberrant expression of MYB results in leukemias and lymphomas

It has been proposed that v-MYB originates from c-MYB, but its expression is driven by a virus LTR which has strong promoter activity, leading to a higher level of v-MYB. Both forms of avian v-MYB (v-MYB and E26) have proteins truncated from the C-terminus of c-MYB (Fig. 1), thus lacking the C-terminus domain of c-MYB, which is a negative regulatory domain (NRD). The higher levels together with the stability of the truncated MYB protein supports the active cell proliferation, blocking differentiation. This NRD domain may keep function of c-MYB in check so that cells can control their biological fate, either proceeding to differentiation or proliferation. Post-translational modifications have been found at C-terminus of c-MYB, including phosphorylation, sumoylation, acetylation

and ubiquitinylation. The degradation of c-MYB is connected to the C-terminus domains. Changes of the phosphorylation sites to alanines considerately inhibited the efficient degradation by WNT-1 and NLK pathway (Kanei-Ishii et al., 2004a). FBXW7α has been shown to interact directly with c-MYB through its WD40 domain and induce the ubiquitination of c-MYB in the presence of NLK, indicating that FBXW7 targets c-MYB for degradation in response to WNT-1 signal pathway. Mutations in FBXW7 identified in T-ALL lines suggest the role of c-MYB in malignancies (Kanei-Ishii et al., 2004a; Kanei-Ishii et al., 2008).

> 60 alternative splice forms of *c-MYB* mRNAs have been found in primary leukemia samples (O'Rourke and Ness, 2008; Zhou et al., 2011). Some of the splice variants correlated with poor survival in a small cohort of precursor B-ALL samples (Zhou et al., 2011), suggesting their potential role as prognostic and diagnostic biomarkers. In another study, the 9A *c-MYB* isoform is overexpressed in Adult T-cell leukemia/lymphoma (ATL) (Nakano et al., 2016). *c-MYB-9A* induced significantly higher transactivation than wild type *c-MYB* on its regulated genes, including critical regulators for cell proliferation and NF-κB, implicating overexpression of this c-MYB variant is associated with disorders in cellular homeostasis and consequently, accelerated transformation, cell proliferation, and malignancy in ATL cells (Nakano et al., 2016).

3.2. High levels of MYB expression in cancer cells

Deregulated expression of *MYB* was first reported in human acute myelogenous leukemia (Westin et al., 1982); (Rosson and Tereba, 1983; Pattabiraman and Gonda, 2013) (Table 2), and subsequently also found in several other malignancies (Biroccio et al., 2001; Greco et al., 2001; Persson et al., 2009) (Table 2). *MYB* is highly expressed in breast, pancreatic and other cancers (Guerin et al., 1990; Biroccio et al., 2001; Drabsch et al., 2007; Zhang et al., 2013); in pancreatic cancer, aberrant expression of *MYB* was found in all malignant cases, but not detectable in normal pancreas (Srivastava et al., 2015). Forced expression of *MYB* promoted cell growth, cell-cycle progression, survival and malignant behavior. Gene expression profile revealed that MYB modulates the expression of genes associated with proliferation, survival and metastasis supporting the role of *MYB* in pancreatic cancer pathogenesis (Srivastava et al., 2015).

Genetic rearrangements (translocations and duplications) of *c-MYB* is frequently found in tumors, including leukemia (Pattabiraman and Gonda, 2013) and adenoid cystic carcinoma (Brayer et al., 2016). These genetic changes are associated with higher *c-MYB* expression presumably due to juxtaposition of a new enhancer in the vicinity of *c-MYB* (Clappier et al., 2007) or a gene dosage effect (Lahortiga et al., 2007). A recurrent t(6;9) (q22–23; p23–24) translocation, which fuses the *MYB* proto-oncogene on chromosome 6q to the *NFIB* gene on chromosome 9p, potentially resulting in the expression of novel *MYB – NFIB* fusion oncogenes, has been reported (Persson et al., 2009; Mitani et al., 2011). Chimeric transcripts predominantly consisting of *MYB* exon 14 linked to the last coding exon(s) of *NFIB* have been detected. It has been proposed that the deletion of conserved target sites for miR-15a/16 and miR-150 microRNAs, important in negative regulation of *MYB*, and over expression of the fusion transcripts and protein, activate critical *c-MYB* targets

including genes associated with apoptosis, cell cycle control, cell growth/angiogenesis, and cell adhesion, contributing to the oncogenic potential of MYB (Persson et al., 2009).

4. *MYB* is essential for hematopoiesis and red cell differentiation

MYB is a key regulator of hematopoiesis and erythropoiesis (Ramsay and Gonda, 2008); (Mucenski et al., 1991). c-MYB plays an essential role in controlling the erythroid cellular proliferation/differentiation balance (Vegiopoulos et al., 2006), sustains proliferation, and a low MYB environment favors accelerated differentiation (Emambokus et al., 2003).

RNA interference (RNAi) and gene knockout experiments provided evidence that c-MYB is essential for hematopoiesis. In earlier studies, Gewirtz and Calabretta (Gewirtz and Calabretta, 1988) demonstrated that exposure of normal human bone marrow mononuclear cells to *c-MYB* antisense RNA resulted in a decrease in both colony size and number. Disruption of *c-Myb* (knockout of exon 6) in mouse by Mucenski et al. (Mucenski et al., 1991) was lethal in mice homozygous for the deletion, while heterozygous mice were phenotypically not distinguishable from wild type mice. *c-Myb*$^{-/-}$ mice exhibit embryonic (primitive) blood formation but die at about day 15 of gestation because of a failure to generate adult (definitive) hemopoiesis. Additional hematopoietic lineages were also affected in these *c-Myb*$^{-/-}$ mice. Clarke et al. differentiated *c-Myb* null ES cells in vitro and showed that primitive unilineage macrophage and erythroid precursor commitment could develop. However, no precursors of definitive hematopoiesis were detected, implicating maturation arrest at early multipotential stages (Clarke et al., 2000).

4.1. MYB in T and B lymphocyte development

Early studies demonstrated that knockout of *c-Myb* impaired development of all lineages of hematopoiesis (Mucenski et al., 1991). *c-MYB* is critical in T lymphocyte development, it promotes the development of helper T cells and blocks the development of cytotoxic T cells (Maurice et al., 2007). The study also showed that GATA-3 is a direct target of c-Myb, based on which Maurice et al. proposed that c-Myb is an important regulator of GATA-3. Nakata et al. (Nakata et al., 2010) provided more details on how c-MYB performs this role: it assembles a transcriptional complex with GATA-3, menin, and MLL that allows GATA-3 to auto-regulate its own expression and to regulate the development and maintain viability of Th2 cells in peripheral blood.

c-MYB plays an important role in the differentiation of lymphocytes from precursor stem cells and deletion of *c-Myb* blocks early T cell development (Allen 3rd et al., 1999). A conditional deletion model demonstrated that *c-Myb* is required for T cell differentiation during different stages T cell development (Bender et al., 2004).

Xiao et la. (Xiao et al., 2007) showed that miR-150 controls *c-Myb* expression in vivo in a dose-dependent manner over a narrow range of miRNA and this dramatically affects lymphocyte development and response. A key mediator in this role appears to be T-bet which is a transcription factor with essential roles in multiple immune lineages, and *c-Myb* has been demonstrated to have a key role in regulating the T-bet-mediated anti-viral program (Piovesan et al., 2017). Deletion of *c-Myb* in mature B cells significantly increased serum

IgG2c and CXCR3 expression by upregulating T-bet. Increased expression of T-bet resulted in aberrant plasma cell differentiation within the germinal center. Chen et al. (Chen et al., 2017) found that miR-150 negatively regulates CD8 T cell memory in vivo by regulating c-Myb levels. Overexpression of miR-150 significantly reduced memory formation and fostered terminal differentiation with reduced c-MYB expression. Knocking out miR-150 resulted in higher levels of c-Myb and disrupted the balance between memory precursor and terminal effector CD8 T cells following acute viral infection. The study also showed that c-Myb regulated genes, such as *Bcl-2* and *Bcl-xL*, were upregulated, suggesting a miR-150-c-Myb survival circuit during memory CD8 T cell development (Chen et al., 2017).

4.2. MYB enhancers regulate fetal hemoglobin (HbF) levels

A set of common single nucleotide polymorphisms (SNPs) at the *HBS1L-MYB* intergenic region in chromosome 6q23 has been consistently identified as highly associated with clinically important human erythroid traits (van der Harst et al., 2012). Prominent among these traits is the persistence of fetal hemoglobin in adults (HbF, measured as % HbF of total hemoglobin or as proportion of red blood cells carrying HbF, '% F cells'). A small number of these SNPs displayed an especially strong association, and are encompassed within a region of about 24 kb (originally termed *HBS1L-MYB* Intergenic Polymorphism block 2 or "HMIP-2"). The causal variants reside in two clusters within the block, at −84 and −71 kb respectively, upstream of *MYB.* The SNPs at these two regions disrupt binding of key erythroid enhancers affecting long-range interactions with *MYB* and *MYB* expression, providing a functional explanation for the genetic association of the 6q *HBS1L-MYB* intergenic region with HbF and F cell levels (Stadhouders et al., 2014) (Fig. 4).

Mouse supporting studies were provided by Suzuki et al. (Suzuki et al., 2013) who reported a mouse model of hereditary persistence of fetal hemoglobin (HPFH) in which a transgene was randomly inserted into the orthologous murine *Hbs1l-Myb* locus. The transgene location corresponded to the −84 kb of human HMIP region. Homozygous transgenic mice (Hbs1l-MybTg/Tg) displayed a marked reduction of *Myb* expression in the megakaryocytic and erythroid lineages, and approximately 4- and 20-fold-higher levels of mouse embryonic εy- and βh1-globins, respectively, than control animals. Studies in mice utilizing ChIP-seq and Chromatin Conformation Capture (3C)-Sequencing showed that Myb activity occurs within an active chromatin hub (ACH) encompassing the enhancers in the *Myb-Hbs1l* intergenic region and the *Myb* promoter and first intron. Downregulation of *Myb* on erythroid differentiation leads to destabilization of the ACH (Stadhouders et al., 2012).

A systemic dissection applying saturating mutagenesis using multiple Cas9 CRISPR genome-editing approach identified 98 DNase I–hypersensitive sites (DHSs) in the HMIP region from erythroid precursors (Canver et al., 2017). The results confirmed the enhancer function of −84 kb and a potential element at −71 kb upstream of *c-MYB*, consistent with previous findings (Thein et al., 2007; Stadhouders et al., 2014). It also identified a novel *c-MYB* enhancer at position −36 and confirmed presence of the other potential elements at positions −7, −83 and −126 kb. Erythroid-specific transcripts were detected in the intergenic region (Wahlberg et al., 2009), that were subsequently shown to be long

non-coding RNA (lncRNA) at the −84 region, in erythroid cells (Morrison et al., 2017). The mechanistics of how the lncRNA affects MYB expression was not shown in the study (Morrison et al., 2017). The conclusion from these studies is that, although regulation of *MYB* expression is via its proximal promoter region (Sullivan et al., 1997) and microRNAs (Lu et al., 2008; Zhao et al., 2009; Sankaran et al., 2011), it is additionally controlled distally by enhancer elements > 80 kb upstream of its promoter, illustrating the high degree of regulatory complexity that governs *MYB* expression.

These studies also established that *MYB* is the relevant gene in the *HBS1L-MYB* region regulating the erythroid traits and fetal hemoglobin levels. Compelling evidence has also been provided that the increased HbF effect is mediated, at least in part, through down-modulation of *MYB* as shown by targeting of its 3′UTR by microRNAs 15a and 16–1 (Sankaran et al., 2011). shRNA studies against c-MYB results in elevated fetal hemoglobin gene expression (Sankaran et al., 2011). Forced expression of *c-MYB* in K562 cells significantly inhibited γ-globin gene expression when compared with the parental cell line or vector controls (Jiang et al., 2006).

How *c-MYB* exactly controls HbF levels and the many other erythroid traits is not yet fully understood. A clear anti-correlation between *MYB* and HbF levels has emerged, which was further confirmed by the reduced *MYB* expression we observed in erythroid cells from high HbF individuals (Jiang et al., 2006). Lower MYB levels were reported to slow down cell cycle progression and to accelerate differentiation kinetics in later stages of erythroid development in mouse and human erythroid cells (Jiang et al., 2006; Bianchi et al., 2010). In accordance with these results, ChIP-seq experiments detected c-Myb binding to key cell cycle regulators (i.e. *Bcl2, Cdk6, Myc*) in murine erythroid progenitors. Furthermore, several of these genes were found to be misregulated in MYB loss-of-function studies in human erythroid progenitors. Accelerated differentiation in an environment of lower MYB levels could favor premature cell cycle termination during the proliferation cycles of adult erythropoiesis, producing more erythroid cells that synthesize predominantly HbF (“F-cells”) before the switch to adult hemoglobin synthesis occurs.

Alternatively, recent studies suggest that the c-MYB transcription factor plays an important role in the emerging TF network governing γ-globin expression, in which the BCL11A and KLF1 proteins play key repressive roles. Analysis of c-MYB loss-of-function studies (Bianchi et al., 2010; Sankaran et al., 2011; Suzuki et al., 2013) indeed showed that several of the c-MYB-bound γ-globin repressor genes (i.e. *BCL11A*, *KLK1*) are downregulated upon MYB depletion. These observations suggest that c-MYB directly activates key γ-globin repressor genes.

5. Summary

MYB is a transcription factor comprising 3 functional domains, DBD, TAD and NRD. It is required for hematopoiesis and essential for life. MYB can interact with many proteins, including p300, a multifunctional protein. p300 has several TAD domains and physically interact with many transcription factors. Both v-MYB and c-MYB are able to bind similar sequences of DNA and the functional difference may be from the protein interaction with

other factors. Aberrant *MYB* expression, rare isoforms and truncated forms of MYB, have been found in human leukemias and solid tumors. Increasing fetal hemoglobin is beneficial for beta hemoglobinopathies, and recent investigations have provided some insight on the role of MYB in fetal hemoglobin gene expression. Dissection of the dynamic *MYB* expression and the dynamic interaction of MYB with a complex network of proteins is challenging but will provide insights on how it may control cell proliferation, differentiation and cell maturation.

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Abbreviations:

MYB	MYB protein
MYB	gene
v-MYB	AMV MYB protein
c-Myb	Myb protein from either mouse or chicken
c-Myb	*Myb* gene from mouse or chicken
DBD	DNA binding domain
TAD	transcription activation domain
NRD	negative regulatory domain
HMIP	HBS1L-MYB intergenic polymorphisms
AMV	avian myeloblastosis virus
HbF	fetal hemoglobin
miRNA	microRNA
SANT	Swi3, Ada2, N-Cor, and TFIIIB
ChIPseq	ChIP sequencing
PEST	proline, glutamic acid, serine, threonine
ATL	Adult T-cell leukemia/lymphoma
ALL	acute lymphoblastic leukemia
AML	acute myelogenous leukemia

CRC	colorectal cancer
ACC	adenoid cystic carcinomas
DHSs	DNase I–hypersensitive sites

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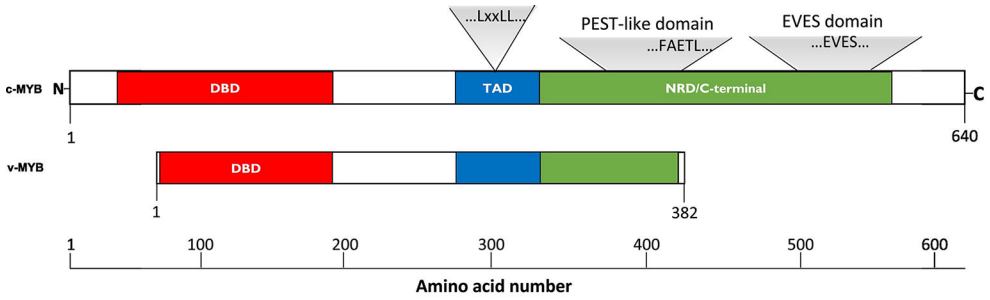

A: Structure and functional domains of c-MYB and v-MYB

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Hs          MARRPRHSIYSSDEDDEDFEMCDHDYDGLLPKSGKRHLGKTRWTREEDEKLKKLVEQNGT     60
Mm          MARRPRHSIYSSDEDDEDIEMCDHDYDGLLPKSGKRHLGKTRWTREEDEKLKKLVEQNGT     60
Gg          MARRPRHSIYSSDDDEEDVEMYDHDYDGLLPKAGKRHLGKTRWTREEDEKLKKLVEQNGT     60
v-Myb       ------------------------------------------------------------     0

Hs          DDWKVIANYLPNRTDVQCQHRWQKVLNPELIKGPWTKEEDQRVIELVQKYGPKRWSVIAK     120
Mm          DDWKVIANYLPNRTDVQCQHRWQKVLNPELIKGPWTKEEDQRVIELVQKYGPKRWSVIAK     120
Gg          EDWKVIASFLPNRTDVQCQHRWQKVLNPELIKGPWTKEEDQRVIELVQKYGPKRWSVIAK     120
v-Myb       -----------NRTDVQCQHRWQKVLNPELNKGPWTKEEDQRVIEHVQKYGPKRWSDIAK     49
                       ****************** ************** ********** ***

Hs          HLKGRIGKQCRERWHNHLNPEVKKTSWTEEEDRIIYQAHKRLGNRWAEIAKLLPGRTDNA     180
Mm          HLKGRIGKQCRERWHNHLNPEVKKTSWTEEEDRIIYQAHKRLGNRWAEIAKLLPGRTDNA     180
Gg          HLKGRIGKQCRERWHNHLNPEVKKTSWTEEEDRIIYQAHKRLGNRWAEIAKLLPGRTDNA     180
v-Myb       HLKGRIGKQCRERWHNHLNPEVKKTSWTEEEDRIIYQAHKRLGNRWAEIAKLLPGRTDNA     109
            ************************************************************

Hs          IKNHWNSTMRRKVEQEGYLQESSKASQPAVATSFQKNSHLMGFAQAPPTAQLPATGQPTV     240
Mm          IKNHWNSTMRRKVEQEGYLQEPSKASQTPVATSFQKNHLMGFGHASPPSQLSPSGQSSV     240
Gg          IKNHWNSTMRRKVEQEGYLQESSKAGLPSATTGFQKSHLMAFAHNPPAGPLPGAGQAPL     240
v-Myb       VKNHWNSTMRRKVEQEGYPQESSKAGPPSATTGFQKSHLMAFAHNPPAGPLPGAGQAPL     169
            :****************** ** ***.   .:*.***..***.*.:  * . *  :**  :

Hs          NNDYSYYHISEAQNVSSHVPYPVALHVNIVNVPQPAAAAIQRHYNDEDPEKEKRIKLEL     300
Mm          NSEYPYYHIAEAQNISSHVPYPVALHVNIVNVPQPAAAAIQRHYNDEDPEKEKRIKLEL     300
Gg          GSDYPYYHIAEPQNVPGQIPYPVALHVNIVNVPQPAAAAIQRHYNDEDPEKEKRIKLEL     300
v-Myb       GSDYPYYHIAEPQNVPGQIPYPVALHINIINVPQPAAAAIQRHYTDEDPEKEKRIKLEL     229
            ..:* ****:* **: .::*******:**:***************.***************

Hs          LLMSTENELKGQQVLPTQNHTCSYPGWHSTTIADHTRPHGDSAPVSCLGEH-HSTPSLPA     359
Mm          LLMSTENELKGQQALPTQNHTCSYPGWHSTSIVDQTRPHGDSAPVSCLGEH-HATPSLPA     359
Gg          LLMSTENELKGQQALPTQNHTANYPGWHSTTVADNTRTSGDNAPVSCLGEHHHCTPSPPV     360
v-Myb       LLMSTENELKGQQALPTQNHTANYPGWHSTTVADNTRTSGDNAPVSCLGEHHHCTPSPPV     289
            *************.*******.*******::.*:**  **.********* *.*** *.

Hs          DPGSLPEESASPARCMIVHQGTILDNVKNLLEFAETLQFIDSFLNTSSNHENSDLEMPSL     419
Mm          DPGSLPEESASPARCMIVHQGTILDNVKNLLEFAETLQFIDSFLNTSSNHESSGLDAPTL     419
Gg          DHGCLPEESASPARCMIVHQSNILDNVKNLLEFAETLQLIDSFLNTSSNHENLNLDNPAL     420
v-Myb       DHGCLPEESASPARCMIVHQSNILDNVKNLLEFAETLQLIDSFLNTSSNHENLNLDNPAL     349
            * *.***************..**************:***********. .*: *:*

Hs          TSTPLIGHKLTVTTPFHRDQTVKTQKENTVFRTPAIKRSILESSPRTPTPFKHALAAQEI     479
Mm          PSTPLIGHKLTP-----CRDQTVKTQKENSIFRTPAIKRSILESSPRTPTPFKHALAAQEI     475
Gg          TSTPVCGHKMSVTTPFHRDQPFKTQKENHVFRTPAIKRSILESSPRTPTPFKNALAAQEI     480
v-Myb       TSTPVCGHKMSVTTPFHKDQTFTEYRKMHGGAV----------------------------     382
             ***: ***::      :** ..  ::      .

Hs          KYGPLKMLPQTPSHLVEDLQDVIKQESDESGIVAEFQENGPPLLKKIKQEVESPTDKSGN     539
Mm          KYGPLKMLPQTPSHAVEDLQDVIKQESDESGIVAEFQESGPPLLKKIKQEVESPTEKSGN     535
Gg          KYGPLKMLPQTPTHLVEDLQDVIKQESEESAIVAGLHESGPPLLKKIKQEVESPTDKAGN     540
v-Myb       ------------------------------------------------------------     382

Hs          FFCSHHWEGDSLNTQLFTQTSPVADAPNILTSSVLMAPASEDEDNVLKAFTVPKNRSLAS     599
Mm          FFCSNHWAENSLSTQLFSQASPVADAPNILTSSVLMTPVSEDEDNVLKAFTVPKNRPLVG     595
Gg          FFCSNHWEGENLNTQLFTHASTMEDVPNLLTSSILKMPVSEEEGSFHKAFAVPRNRPLAS     600
v-Myb       ------------------------------------------------------------     382

Hs          PLQPCSSTWEPASCGKMEEQMTSSSQARKYVNAFSARTLVM       640
Mm          PLQPCSGAWEPASCGKTEDQMTASGPARKYVNAFSARTLVM       636
Gg          PMQHLNNAWESASCGKTEDQMALTDQARKYMAAFPTRTLVM       641
v-Myb       -----------------------------------------       382
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B: Alignment of MYB proteins in Humans, mouse, chicken and AMV

Fig. 1. MYB proteins.

A: Structure and functional domains of c-MYB and v-MYB.

The schematic structure of c-MYB and its functional domains were drawn according to NCBI webpage, https://www.ncbi.nlm.nih.gov/protein/NP_005366.2? report=graph. DBD: DNA binding domain; TAD: transcription activation domain; NRD: negative regulatory domain. The locations for LxxLL, FAETL and EVES motives are depicted. v-MYB lacks NRD in the C-terminus, and hence, it is not surprising that it functions as a transcriptional activator all the time, a property that likely contributes to its role in leukemogenesis.

B: Alignment of MYB proteins in human, mouse, chicken and AMV.

The MYB proteins were aligned from Human (Hs for *Homo sapiens*, NP_005366.2), mouse (Ms for *Mus musculus*, NP_034978.3), chicken (Gg for *Gallus gallus*, P01103.1) and AMV (AAB31930.2). The identical residuals were marked as *, similar residuals were labeled as . or: The alignment was performed with software Clustal2.1. Motif sequences, “LxxLL”, “FAETL” and “EVES” are boxed.

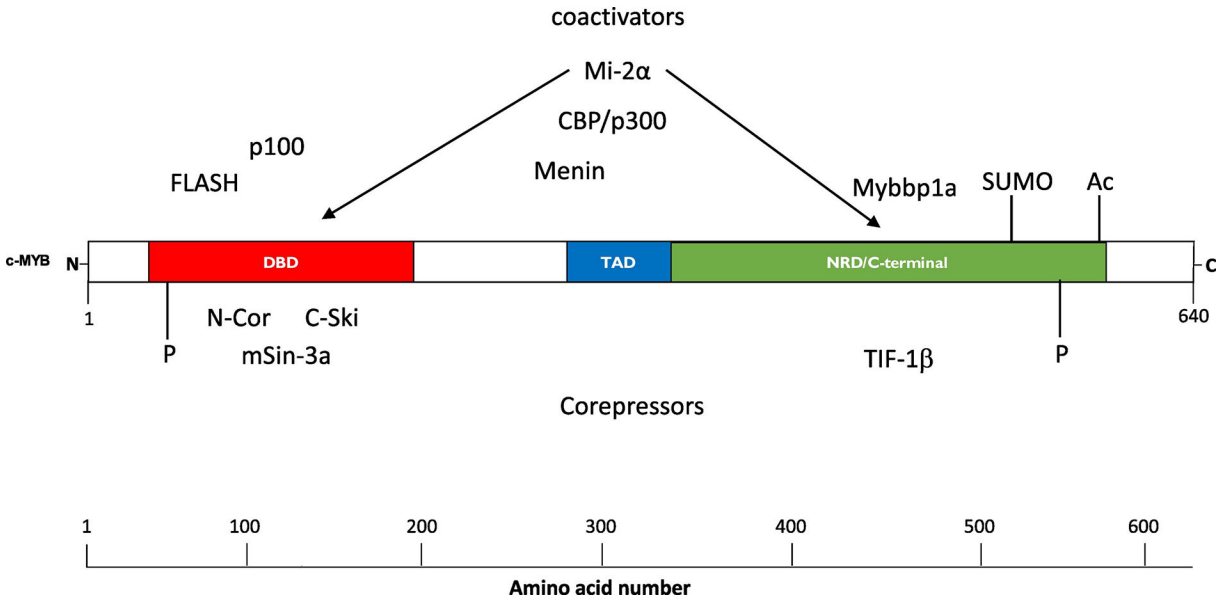

Fig. 2. MYB interaction with other proteins.

For a detailed list of the 50 interacting proteins, please refer to webpage https://thebiogrid.org/. Coactivators are shown above MYB protein and corepressors, below. P: phosphorylation sites; Ac: acetylation; SUMO: SUMOylation. Only some of the 50 proteins interacting with MYB are indicated here; they include FLASH (Alm-Kristiansen et al., 2008), p100 (Leverson et al., 1998), Mi-2α (Saether et al., 2007), CBP/p300 (Pattabiraman et al., 2014), Menin (Nakata et al., 2010) Mybbp1a (Perrera et al., 2010), N-Cor, C-Ski, mSin-3a and TIF1β (Nomura et al., 2004). The modification sites are shown as phosphorylation (Luscher et al., 1990; Aziz et al., 1995), acetylation (Tomita et al., 2000) and SUMOylation (Bies et al., 2002).

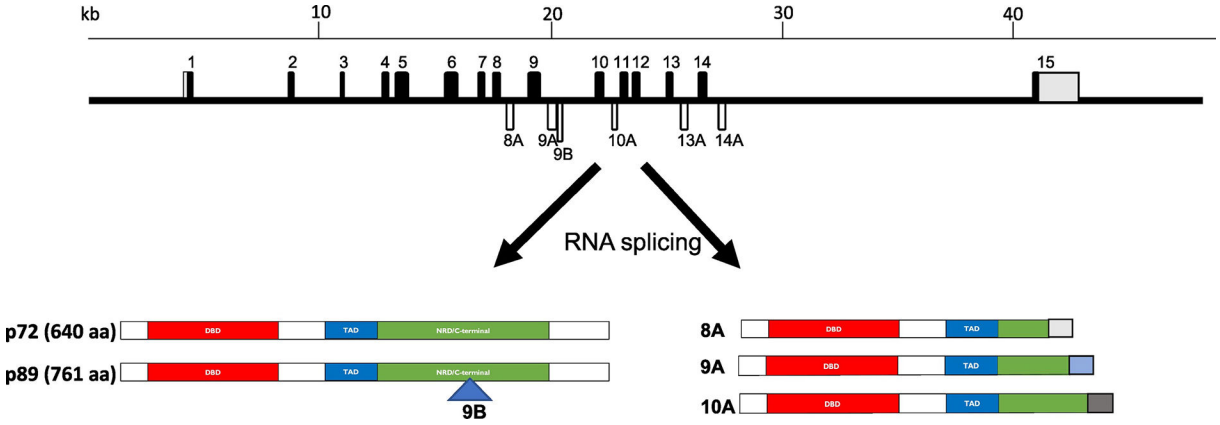

Fig. 3. Transcripts of *c-MYB* and its isoforms.

Transcripts of human *c-MYB*. The top part is schematic of human *MYB* gene structure. The black boxes are exons and the lines between exons are introns. The numbers indicated the exon numbers. The grey parts of exons are non-translated regions. The open boxes are alternative splicing exons. The lower part showed a few transcripts from different splicing (for more details, refer to (Zhou et al., 2011)). The major MYB isoform in human erythroid cells is 72 kD with 640 amino acids (NCBI Reference Sequence: NP_005366.2).

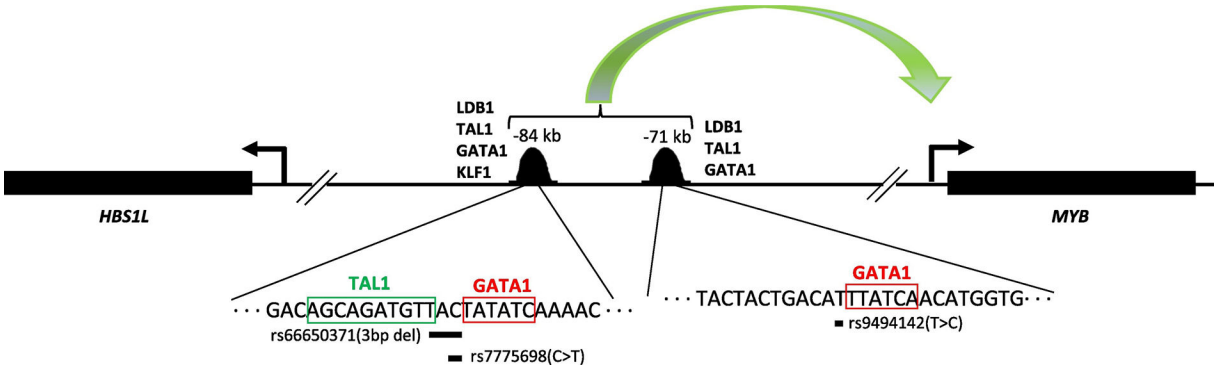

Fig. 4.

HBS1L – MYB intergenic region on chromosome 6q23 with the 2 enhancer sites encompassing the SNPs associated with fetal hemoglobin levels in adults. Schematic structure (not to scale) of *HBS1L* and *MYB* region is depicted. The transcription direction of *HBS1L* and *MYB* are indicated with black arrows. The peaks at −84 and − 71 are from transcription factor (as indicated) binding data (Stadhouders et al., 2014). The zoomed in parts show DNA sequence at −84 and − 71 upstream of the transcription start site of *MYB*. The consensus sequences for TAL1 and GATA1 are labeled and boxed. The three SNPs associated with fetal hemoglobin levels in adults are indicated. The green arrow shows the interactions between the enhancers and proximal promoter.

Table 1.

Orthologs of MYB.

UniProt number	UniProt Entry name	Organism	Gene names	Protein names	Length (amino acids)	Mass (kD)
P10242	MYB_HUMAN	*Homo sapiens* (Human)	*MYB*	Transcriptional activator MYB (Proto-oncogene c-MYB)	640	72.35
P06876	MYB_MOUSE	*Mus musculus* (Mouse)	*Myb*	Transcriptional activator Myb (Proto-oncogene c-Myb)	636	71.44
A0A0G2JV86	A0A0G2JV86_RAT	*Rattus norvegicus* (Rat)	*Myb*	Transcriptional activator Myb (Proto-oncogene c- Myb)	626	70.63
P01103	MYB_CHICK	*Gallus gallus* (Chicken)	*Myb*	Transcriptional activator Myb (Proto-oncogene c-Myb)	641	72.48
P01104	MYB_AVIMB	Avian myeloblastosis virus	*v-Myb*	Transforming protein Myb	382	43.07

Table 2

Aberrant/abnormal MYB in human leukemia and cancers.

Leukemia/cancers	Abnormities	References
AML	*MYB* overexpression, detected by hybridization with v-amv nick translated DNA	(Westin et al., 1982)
Childhood myeloid leukemia	*MYB overexpression, amplification in locus*	(Rosson and Tereba, 1983)
Acute Myelogenous Leukemia (AML)	*MYB* overexpression, amplification in locus	(Pelicci et al., 1984)
AML, ALL	*MYB* overexpression	(Ferrari et al., 1985)
T-cell leukemia cell lines (PEER and MOLT-4)	*MYB overexpression, amplification in locus*	(Ohyashiki et al., 1988)
T-ALL-derived cell lines	*MYB overexpression, amplification in locus*	(Siegert et al., 1990)
Non-Hodgkin lymphoma	*MYB* overexpression	(Okada et al., 1990)
T-ALL cell line CCRF-CEM	*MYB* promoter rearrangement	(Jacobs et al., 1994)
Leukemia cell line TK-6 derived from CML patient with T-cell blast crisis	*MYB truncation*	(Tomita et al., 1998)
Pediatric T-ALL	Recurrent translocation involving *MYB*	(Sinclair et al., 2005)
T-ALL	Recurrent genomic duplication of *MYB* locus	(Clappier et al., 2007); (Lahortiga et al., 2007)
T-ALL	Recurrent translocation involving *MYB*	(Clappier et al., 2007)
T-ALL	Alu-mediated *MYB* tandem duplication	(O'Neil et al., 2007)
T-cell leukemia	Double minute chromosomes containing *MYB*	(Kawamata et al., 2009)
AML harboring MYST3-translocations	Genomic gain in *MYB* locus	(Murati et al., 2009)
Infant acute basophilic leukemia	Recurrent translocation involving *MYB*	(Quelen et al., 2011)
AML-M5	Recurrent translocation involving *MYB*	(Belloni et al., 2011)
T-ALL	Mutation creates a super-enhancer upstream of the TAL1 by *MYB*	(Mansour et al., 2014)
T-ALL	Mutations at *LMO* promoter created *MYB, ETS1* and *RUNX1* binding	(Rahman et al., 2017); (Hu et al., 2017)
Colon carcinoma cell lines	*MYB* aberrantly overexpression	(Alitalo et al., 1984)
Colon adenocarcinoma cell line	*MYB* overexpression	(Winqvist et al., 1985)
Colon carcinoma	*MYB* overexpression	(Torelli et al., 1987)
Colorectal carcinoma cell lines	*MYB* overexpression	(Trainer et al., 1988)
Colon cancer cell lines, colon tumors	*MYB* aberrantly overexpression	(Untawale and Blick, 1988)
Colon carcinoma cell line Colo 205	*MYB* overexpression	(Melani et al., 1991)
Colonic adenomatous polyps	*MYB* overexpression	(Ramsay et al., 1992)
Colon carcinoma cell lines	*MYB* overexpression from mutations at attenuator	(Thompson et al., 1997)

Leukemia/cancers	Abnormities	References
Colorectal cancer (CRC)	*MYB* deregulated	(Biroccio et al., 2001)
CRC	*MYB* aberrantly overexpression	(Biroccio et al., 2001)
Colon tumor	*MYB* deregulated	(Greco et al., 2001)
CRC	mutation in poly-T track of *MYB* intron 1 allowed its high expression	(Hugo et al., 2006)
CRC	*MYB* overexpression	(Tichy et al., 2016)
Esophageal adenocarcinoma	*MYB* overexpression	(Brabender et al., 2001)
Pancreatic cancer cells	*MYB* aberrantly overexpression	(Srivastava et al., 2015)
Breast cancer	*MYB* overexpression, 29% in BRCA1 mutations	(Kauraniemi et al., 2000)
Adenoid cystic carcinomas (ACC) (breast, head and neck)	*MYB-NFIB* gene fusions, lost miRNA target sequence	(Persson et al., 2009)
ACC (salivary gland, sinonasal cavity, tracheobronchial tree, larynx, breast, and vulva)	*MYB-NFIB* gene fusions	(Brill 2nd et al., 2011)
Breast denoid cystic carcinomas	*MYB-NFIB* gene fusion	(D'Alfonso et al., 2014)
Breast carcinoma	*MYB* overexpression	(Li et al., 2016)
Pediatric brain tumors	*MYB* rearrangements	(Zhang et al., 2013)
ACC (salivary gland)	*MYB-NFIB* gene fusion	(Hudson and Collins, 2014)
ACC (salivary gland and others)	*MYB-NFIB* rearrangements	(Togashi et al., 2018)