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REVIEW

From modulation of cellular plasticity to potentiation of therapeutic resistance: new and emerging roles of MYB transcription factors in human malignancies

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Abstract
MYB transcription factors are encoded by a large family of highly conserved genes from plants to vertebrates. There are three members of the MYB gene family in human, namely, *MYB*, *MYBL1*, and *MYBL2* that encode MYB/c-MYB, MYBL1/A-MYB, and MYBL2/B-MYB, respectively. MYB was the first member to be identified as a cellular homolog of the v-myb oncogene carried by the avian myeloblastosis virus (AMV) causing leukemia in chickens. Under the normal scenario, MYB is predominantly expressed in hematopoietic tissues, colonic crypts, and neural stem cells and plays a role in maintaining the undifferentiated state of the cells. Over the years, aberrant expression of MYB genes has been reported in several malignancies and recent years have witnessed tremendous progress in understanding of their roles in processes associated with cancer development. Here, we review various MYB alterations reported in cancer along with the roles of MYB family proteins in tumor cell plasticity, therapy resistance, and other hallmarks of cancer. We also discuss studies that provide mechanistic insights into the oncogenic functions of MYB transcription factors to identify potential therapeutic vulnerabilities.

Keywords MYB · Transcription factors · Gene alterations · Cancer cell plasticity · Epithelial-mesenchymal transition · Therapy resistance

1 Introduction

MYB transcription factors are encoded by a large family of highly conserved genes from plants to vertebrates, suggesting their significance in the fundamental biological processes [1, 2]. In humans and other vertebrates, there are three members in the *MYB* gene family, namely, *MYB*, *MYBL1*, and *MYBL2* encoding MYB or c-MYB, A-MYB or MYBL1, and B-MYB or MYBL2, respectively. Invertebrates, however, harbor a single *Myb* gene only [1]. *MYB* was the first member to be identified in humans as a cellular homolog of the *v-myb* oncogene inserted in the genome of avian myeloblastosis virus (AMV) causing acute myeloblastic leukemia in chickens [3, 4]. Later, screening of T-cell cDNA libraries with low stringency hybridization with a c-myb probe identified *A-MYB* and *B-MYB* genes showing strong sequence homology [5, 6]. *MYB* is predominantly expressed in hematopoietic tissues, colonic crypts, and neural stem cells, whereas *MYBL1* expression is restricted to gonadal tissue, germinal B lymphocytes, developing mammary gland, and central nervous system. In contrast, the expression of *MYBL2* is ubiquitous in all proliferating cells [7, 8]. An aberrant expression of *MYB* genes has been reported in different cancers due to either gene amplification and/or transcriptional upregulation. Alternative splice variants and gene fusions of *MYB*, *MYBL1*, and *MYBL2* have also been reported in some cancers [2, 9–11]. This review article sheds light on various MYB alterations reported in cancer along with the roles of MYB family proteins

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in tumor cell plasticity and therapy resistance sustaining the relentless growth and spread of cancer cells. We also discuss studies that provide insights into these oncogenic functions of MYB transcription factors to identify potential therapeutic vulnerabilities.

2 Genomic and proteomic organization of MYB transcription factors

According to UCSC genome browser (https://genome.ucsc.edu/), *MYB* gene is present at the chromosomal band 6q23.3 as a 37,865 bp long sequence containing 16 exons and 15 introns. *MYBL1* is localized on chromosome 8 in the region q13.1 and is the largest in size (51,044 bp), also consisting of 16 exons and 15 introns. The chromosomal locus of *MYBL2* is 20q13.12 and its size is 49,369 bp containing 14 exons and 13 introns (Fig. 1A). A large number of splice variants of *MYBs* are reported, of which some are translated, while others undergo non-sense-mediated decay or their fates remain unknown [12]. Full length MYB protein is composed of 642 amino acids having a molecular weight of ~ 75 kD. A-MYB/MYBL1 and B-MYB/MYBL2 are slightly heavier, weighing about 95 kD and 93 kD, and are composed of 752 and 742 amino acids, respectively [2]. Structurally, all MYB proteins have large similarities. They contain a highly conserved N-terminal DNA-binding domain (DBD), encompassing three tryptophan-rich tandemly repeated motifs of ~ 50 amino acids (R1, R2, and R3), a central trans-activated domain (TAD), and a C-terminal negative regulatory domain (NRD). The folding architecture is similar for each of the three repeats of DBD and each repeat contains a variation of helix-turn-helix (HTH) motif [13, 14] (Fig. 1B).

All MYB proteins, including v-myb, recognize and bind to the same DNA consensus sequence [5′-(YAACG/TG)-3′], known as the MYB recognition or MYB-binding site (MBS). "Y" in this sequence represents a pyrimidine base (C or T) [15, 16]. Structural analysis has revealed that R2 and R3 motifs are responsible for DNA recognition, while the R1 motif is dispensable [13, 17]. Both c-MYB and A-MYB share similarities in the nature of amino acid composition of TAD, having clusters of acidic amino acids, although there are some sequence-specific differences [18]. B-MYB TAD shows minimal homology to that of c-MYB despite containing the clusters of acidic residues indicating functional differences in gene activation [19]. Across different species, C-terminal regulatory domain shows conserved sequences, with most significant similarity observed in the central region [20, 21]. This domain contains a leucine zipper structure, which confers negative regulatory activity by forming a homodimer that interferes with the binding to the target DNA sequence [22–24]. Post-translational modifications in the regulatory

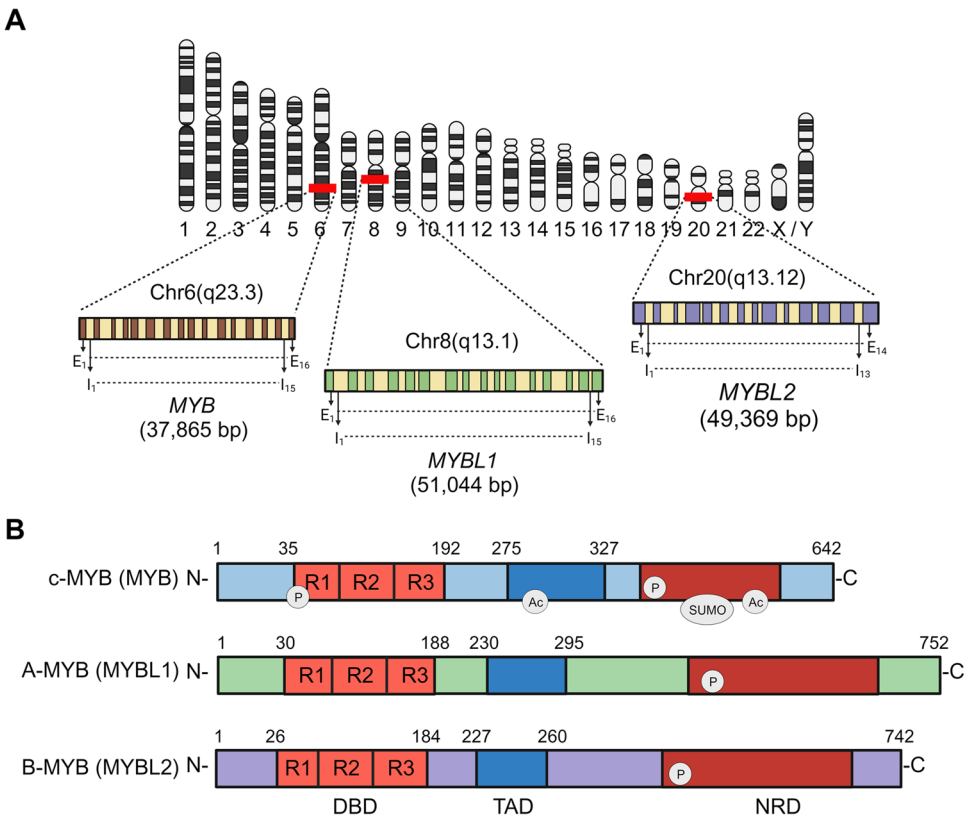

Fig. 1 Genomic and proteomic organization of MYB transcription factors. **A** Genomic location of MYB transcription factors (MYB, MYBL1, and MYBL2) and depiction of their exons (E) and introns (I). **B** Comparative presentation of functional domains of MYBs. The N-terminal DNA binding domain (DBD) of MYB, MYBL1, and MYBL2 is composed of approximately ~ 150 amino acids and consists of three repeats, R1, R2, and R3. The central region contains transactivation domain (TAD), with different number of amino acids in MYB (~ 135 a.a.), MYBL1 (~ 65 a.a.) and MYBL2 (~ 33 a.a.). C-terminal negative regulatory domain (NRD) has variable number of amino acids in different MYB proteins and frequently undergoes posttranslational modifications, including phosphorylation (P), acetylation (Ac), and sumoylation (SUMO)

domain inhibit its interaction with DBD, thus repressing the transcriptional activity [25–27]. Consequently, truncation or mutations in this domain are known to confer oncogenic ability to MYB resulting from its constitutive activation [28].

3 MYB alterations in cancers

While the expression of MYB family proteins is tightly regulated in healthy tissues, a number of alterations have been reported in human malignancies. These include gene amplification, mutations, and structural rearrangements due to chromosomal translocation or gene fusion resulting in their enhanced biological activity that promotes different aspects of tumorigenesis.

3.1 Gene copy number alterations

Analysis of candidate oncogenes in pancreatic cancer (PC) identified amplification at 6q24 chromosomal locus that houses *MYB* [29]. Similarly, a copy number gain of *MYB* was also detected in *BRCA1*-mutated breast tumors by fluorescence in situ hybridization analysis of 6q22-24 region [30]. An amplification of *MYB* has also been reported in pediatric low-grade gliomas (LGGs) [31]. High-density profiling of gastric adenocarcinomas revealed somatic copy number alterations in *MYB* oncogene associated with its overexpression [32]. Similarly, *MYB* amplification has also been reported in prostate cancer exhibiting enhanced amplification frequency as it progressed from hormone-sensitive to hormone-resistant state [33]. Amplification of *MYB* is reported to be of prognostic significance in esophageal carcinoma [34]. Pediatric low-grade gliomas (PLGGs) have the most significant gain in 8q13.1 chromosomal region resulting in the partial duplication of *MYBL1* along with the deletion of its c-terminal negative-regulatory domain [35]. *MYBL2* overexpression in breast cancer, malignant melanoma, and sporadic ovarian cancer is also shown to partly result from the amplification of 20q13 locus [36–39].

3.2 Gene mutations

Bioinformatics analysis of *MYB* (*MYB*, *MYBL1*, and *MYBL2*) genes predicted a total of 45 non-synonymous single-nucleotide polymorphisms (nsSNPs) associated with the high risk of cancer. Some of these mutations, which were located within the helix-turn-helix (HTH) domain, were predicted to be conserved and associated with a shift in DNA-binding specificity of the protein leading to altered protein function [40]. In another study, SNPs (rs619289, rs826943, and rs826944) in *MYBL2* promoter regions were identified and associated with an increased susceptibility of breast cancer [39].

3.3 Chromosomal translocations

Another type of alteration in *MYB* genes results from chromosomal translocation. One among these is the translocation t(6;9) leading to the fusion of *MYB* and *NFIB* genes, which generates a chimeric transcripts consisting of exon 14 of *MYB* fused with the last coding exon of *NFIB*. This fusion product lacks MYB 3′UTR containing the binding sites for negative regulatory microRNAs leading to the overexpression of the chimeric MYB-NFIB transcript and protein [41, 42]. Such fusions have been detected in primary and metastatic Adenoid Cystic Carcinoma (AdCC) of salivary gland resulting in the overexpression of multiple chimeric variants [43]. Genomic analysis of pediatric low-grade gliomas (PLGG) identified *MYB:QK1* fusion transcript that results in MYB activation due to the truncation of c-terminal negative regulatory domain and hemizygous loss of tumor suppressor *QK1* expression [44]. More recently, *MYB:QK1* fusion was also identified in pediatric high-grade glioma and adult angiocentric glioma (AG) [45]. Massively parallel sequencing analysis of breast adenoid cystic carcinoma lacking the *MYB-NFIB* fusion has identified the gene rearrangement in *MYBL1*, such as *MYBL1-ACTN1* and *MYBL1-NFIB*, associated with its overexpression [46]. In addition, a novel MYBL1-NFIB gene fusion as a result of t(8;9) translocation and multiple other rearrangements in the *MYBL1* gene has been reported [47]. A fusion transcript of *MYBL1* and *RAD51B* of unknown functional significance is also reported in AdCC resulting from t(8;14) translocation. This fusion leads to antisense transcription of part of the *RAD51B* intron and truncation of the MYBL1/ A-MYB in the predicted fusion protein [10].

4 Multifaceted roles of MYB proteins in oncogenesis

Cancer development is a multistep process where the transformed cell gains unrestricted proliferation and survival abilities, becomes invasive, leaves the primary site, and establishes itself at secondary locations. This gradual process of evolution is facilitated by accumulation of a series of molecular alterations that work in concert influenced by the external microenvironment [48]. Among these, MYB proteins appear to play a central role in multiple malignancies by affecting the multiple aspects of cancer development as discussed below:

4.1 Cellular plasticity

The earliest work on MYB demonstrated its restricted expression in stem cells and later it was shown that it plays an essential role in the maintenance of the undifferentiated

state [49–51]. Restored expression of *MYB* family genes in several malignancies suggests that it might play a similar role to support continued evolution of cancer. Indeed, cancer cells must exhibit adaptive capabilities to sustain their existence under constantly changing microenvironmental conditions. Thus, cellular plasticity is an important attribute that allows cancer cells to survive when they face stressful situations. Epithelial to mesenchymal transition (EMT), an evolutionarily conserved process involved in normal embryonic development and tissue regeneration, bestows such property to the cancer cells [52]. Almost a couple of decades ago, Dvorak et al. reported the role of MYB in the induction of EMT in trunk neural crest cells [53]. Later, Tanno et al.'s group demonstrated that MYB induced the mesenchymal phonotype in embryonic kidney and neuroblastoma cells *via* transcriptional upregulation of Slug (*SLAI2*) [54]. The same group later showed that TGFβ-induced EMT in ER(+) breast cancer cells was mediated through MYB, which enhanced the expression of Slug and Bcl-2 [55]. TGFβ/MYB axis is also shown to promote EMT phenotype in esophageal cancer cells [56]. Along with these observations, we also found a role of MYB in EMT in prostate cancer cells [57]. Moreover, in a very recent study, we have observed that MYB plays an essential role in metabolic plasticity of pancreatic cancer cells, especially when these cells are exposed to hypoxia. MYB induced the expression of several glycolytic genes through direct promoter binding and by enhancing the recruitment of HIF-1α on the shared target gene promoters [58].

MYB is crucial for the activation of discoidin domain receptor 2 (DDR2), a key player in matrix stiffness- induced EMT. It has been shown that increased cellular contractility on a stiff matrix recruits MYB and LEF1 to DDR2 promoter and promotes the expression of mesenchymal markers [59]. The aberrant expression of c-MYB has been reported in colorectal cancer (CRC), and its knockout inhibits EMT in CRC cells *via* a mechanism involving c-fos repression [60]. A negative correlation of MYB with E-cadherin and positive correlation with vimentin in salivary adenoid cystic carcinoma (SACC) also suggests its association with EMT [61]. Single-cell RNA sequencing of metastatic cells from the lungs of hepatoblastoma patients revealed distinct transcriptional signature and significant association of *MYBL2* expression with poor prognosis of patients. Overexpression of *MYBL2* in hepatoblastoma cancer cells (HCC) promoted the SNAI1 expression and Smad2/3 phosphorylation thereby promoting the EMT and tumorigenesis [62]. A higher expression of *MYBL2* has also been reported in metastatic breast cancer cells and aggressive triple-negative subtype (TNBC) and shown to promote EMT [36, 63, 64]. *MYBL1* also transcriptionally upregulates *TWIST1*, a promoter of EMT, in HCC cells [65]. These findings establish that MYB proteins afford cellular plasticity to cancer cells either directly and/or by altering the expression and transcriptional activity of other transcription factors to support their adaptive nature under harsh environments (Fig. 2).

4.2 Cell proliferation and survival

EMT not only imparts aggressive behavioral properties to the cancer cells but also supports their survival. In addition, uncontrolled cell division is a crucial biological process that

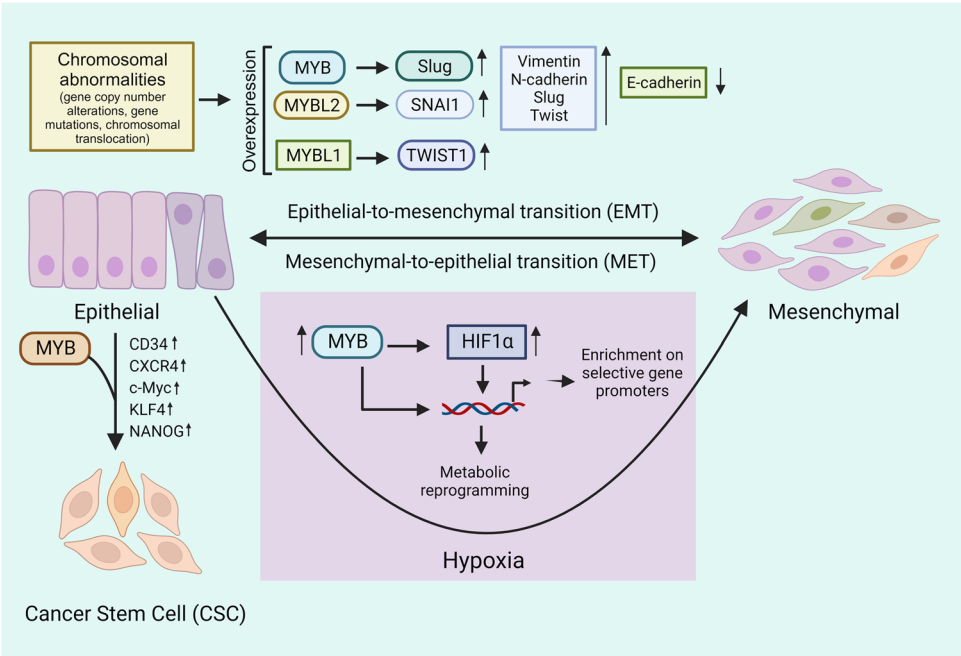

Fig. 2 Role of MYB family proteins in cancer cell plasticity. Aberrant expression/activation of MYB proteins promotes epithelial-to-mesenchymal transition either directly modulating the expression of relevant genes or by modulating the expression of known inducers of EMT such as, Slug, SNAI1, and TWIST1. In addition, MYB also regulates the expression of stem cell-associated proteins, including CD34, CXCR4, c-MYC, KLF4, and Nanog, to impart stemness properties. Under hypoxic conditions, MYB expression is induced and interacts with HIF1α to coordinately regulate gene expression associated with metabolic reprogramming

promotes cancer burden at the primary site and its establishment at the secondary metastatic sites. A very early report on MYB function demonstrated that MYB transcript levels are transiently increased *via* post-transcriptional mechanism during cell cycle progression in various cell types [66]. Later, this important function of MYB was confirmed by suppressing its expression that resulted in significantly decreased proliferation of myeloid-leukemia cells [67]. Gonda and colleagues demonstrated that MYB is regulated by estrogen/ER signaling and plays a role in the proliferation and survival of ER + breast cancer cells [68]. Transgenic knockout of *MYB* in murine models of breast cancer revealed its essential role in mammary tumorigenesis and cell survival. MYB promoted the expression of survival associated genes; Bcl-2 and GRP78/BiP in breast cancer cells compared to mammary epithelial cells [69]. In acute myeloid leukemia cells, MYB suppression promoted apoptosis and decreased cell survival due to enhanced expression of pro-apoptotic DRAK2 and increased caspase-9 activity [70]. Indeed, chromatin immunoprecipitation coupled with genome promoter tilling microarrays has demonstrated MYB binding to several gene promoters, including those involved in cell-cycle regulation and survival [71].

We have also found a role of MYB in cell cycle progression and survival of pancreatic and prostate cancer cells [57, 72, 73]. Recently, we have shown MYB expression is regulated by androgens in a bi-phasic manner mediating its growth-promoting and -suppressive effects [74]. At lower doses, androgens transcriptionally upregulated MYB whereas at high doses, androgens induced the expression of MYB-targeted miRNA miR-150 leading to its repression. The ubiquitous expression of B-MYB in proliferating cells and its regulation by E2F, a cell cycle-related transcription factor, suggest its important function in cell proliferation [75]. Indeed, the elevated MYBL2/B-MYB expression is shown to promote proliferation of bladder [76], liver [77], and lung [78] cancer cells through upregulation of cell-cycle-associated genes. EGFR signaling co-operates with E2F to enhance *MYBL2* expression and promotes the proliferation of breast cancer cells [79]. *MYBL2* silencing is also shown to inhibit the proliferation of myeloid or lymphoid cells [80]. There are, however, not many reports on the role of MYBL1/A-MYB. The expression of A-MYB is detected in proliferating B-cells, in the S and G2/M phases of the cell cycle, but not in the resting stage suggesting its role in cell cycle progression [81].

4.3 Invasion and metastasis

Most cancer deaths occur due to metastasis, which interferes with the vital organ functions. These attributes are also facilitated through EMT affording invasive capabilities to the cancer cells. A variety of reports have documented the role of MYB in behavioral properties that support the metastatic spread of the cancer cells (Fig. 3). MYB interacts with Wnt effector β-catenin and co-activates the downstream target genes involved in invasion and metastasis of breast cancer cells [82]. Ectopic expression of MYB in human and murine mammary cancer cells is also shown to enhance their potential to invade the Matrigel® by inducing the expression of cathepsin D and MMP9 but downregulating MMP1 [83]. By gain and loss of function studies and using an orthotopic mouse model, we have also demonstrated that MYB promotes invasiveness and metastatic spread of pancreatic cancer cells to the liver, lung, and spleen [72]. MYB knockout in colorectal cancer cells is also shown to inhibit the invasion and metastasis *in vivo* through a mechanism mediated through the repression of c-fos-induced EMT [60]. Interestingly, another report that measured MYB expression in CRC specimens showed its higher expression in primary lesions relative to the distant metastases [84]. This may suggest that likely tumor cells underwent a reversal of EMT facilitated through MYB downregulation as they established themselves at the secondary site.

MYBL2 expression is upregulated in bladder cancer (BLCA), the most common malignancy associated with urinary tract system. Silencing of *MYBL2* inhibited the migration and invasion of bladder cancer cells *in vitro* and reduced lung metastases *in vivo*. These processes involved the interaction of MYBL2 with FOXM1 and transactivation of CDCA3, a protein that could promote Wnt/β-catenin signaling, thus malignant phenotype of BLCA cells [76]. Overexpression of *MYBL2* is also detected in non-small-cell lung cancer (NSCLC) and associated with advancing pathological grades and clinical stages. Using gene knockdown and overexpression approaches, it was shown that MYBL2 was involved in cell migration and invasion. RNA-seq analysis revealed an overexpression of various critical genes involved in cancer metastasis, likely through MYBL2-mediated activation of Erk and Akt signaling pathways [85]. In hepatocellular carcinoma, MYBL1/TWIST1 axis promoted aggressive behavior and metastasis *in vitro* and *in vivo* [65]. In another report, MYBL1 was shown to cause transcriptional upregulation of ANGPT2 to support neovascularization and metastasis in hepatocellular carcinoma [86].

4.4 Therapy resistance

Therapy resistance in cancer can develop through a variety of innate and acquired mechanisms, including the activation of drug efflux transporters, cell death inhibition (apoptosis suppression), altered drug metabolism, genetic and epigenetic modifications of drug targets, upregulation of DNA repair activity, and activation of bypass pathways [87]. A number of studies have shown the significant role of MYB proteins in supporting the cancer survival can be a major

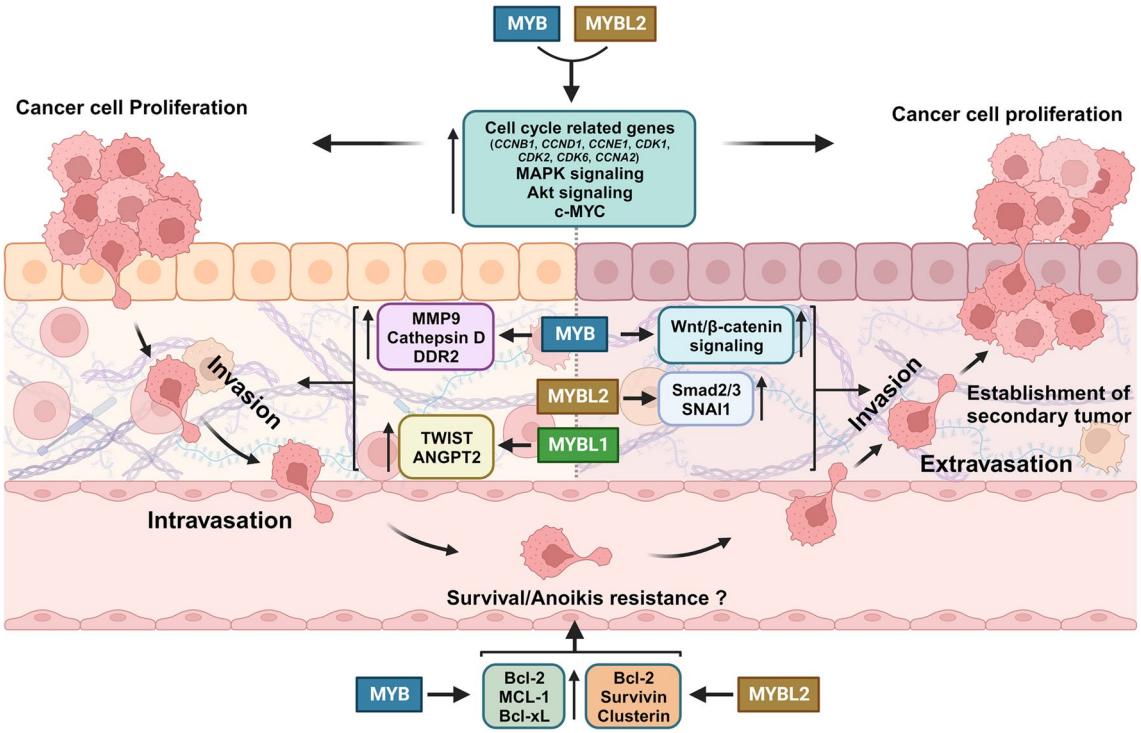

Fig. 3 Impact of MYB oncoproteins on various aspects of cancer cell growth and metastasis. MYB transcription factors play crucial roles in the regulation of proliferation, growth, invasion, and metastasis in various cancer types. MYB and MYBL2 are shown to promote cell proliferation by inducing the expression of cell cycle-related genes, c-MYC, and supporting the activation signaling cascades responsible for proliferation of the tumor cells at the primary and metastatic sites. MYB transcription factors also promote invasion and metastasis of cancer cells by increasing the expression of proteins involved in the degradation of extracellular matrix (MMP9, Cathepsin D), acquisition of migratory phenotype (DDR2, Wnt/β-catenin signaling, Smad2/3 SNAI1, TWIST, and ANGPT2) and likely anoikis resistance through upregulation of survival-associated genes (Bcl-2, MCL-1, Bcl-xL, Survivin, and Clusterin)

roadblock in the efficacy of anticancer drugs (Fig. 4). Indeed, a higher expression of MYB is reported in derived cisplatin-resistant colorectal cancer cells as compared to the parental cells and its silencing led to the increased sensitivity towards cisplatin-mediated toxicity [88]. Similarly, in another report, overexpression of MYB is shown to activate NF-κB and STAT3 signaling in ovarian cancer cells as a mechanism of cisplatin resistance [89]. In comparison to naïve parental MCF-7 cells, tamoxifen-resistant MCF-7 (TAM-MCF7) breast cancer cells show an upregulated expression of MYB. Repression of MYB in these cells re-sensitized them to the tamoxifen treatment [90]. MYB is also shown to regulate DNA damage and components of the homology-directed repair pathway in ER + ve breast cancer cells suggesting that MYB inhibition along with induction of DNA damage could yield improved therapeutic outcomes [91]. In nasopharyngeal cancer cells, overexpression of c-MYB promotes the resistance to apoptosis induced by ionizing radiation by regulating the PARP cleavage and cleaved caspase-3 [92]. A study from Pekarcikova et al. demonstrated the importance of c-MYB/NOX1/p38 signaling axis in chemoresistance of colorectal cancer cells. Ectopic expression of *MYB* protected these cells from oxaliplatin- and doxorubicin-induced apoptosis *via* activation of NOX-1 and p38 MAPK pathway [93]. In glioblastoma cells, ZEB1 is shown to promote *MYB* expression by downregulating miR200, a MYB-targeting microRNA, which in turn, promotes the expression of O-6-methylguanine-DNA methyltransferase (MGMT) to promote chemoresistance [94].

Androgen deprivation therapy (ADT) or castration therapy (CT) has been the mainstay treatment for the advanced and metastatic prostate cancer [95]. Despite an initial response, prostate cancer relapses in most patients as a castration-resistant disease through aberrant activation of androgen receptor (AR) signaling [96]. In our studies, we found that MYB-overexpressing prostate cancer cells survived well under androgen-deprived condition and retained the expression of AR-responsive gene, KLK3/PSA [57]. Later, we demonstrated that MYB interacted with AR and retained it in the nucleus to sustain its transcriptional activity under androgen-reduced condition. Further, these findings were confirmed in an orthotopic model by castrating the mice. We observed that MYB-overexpressing cells sustained their growth following castration and quickly

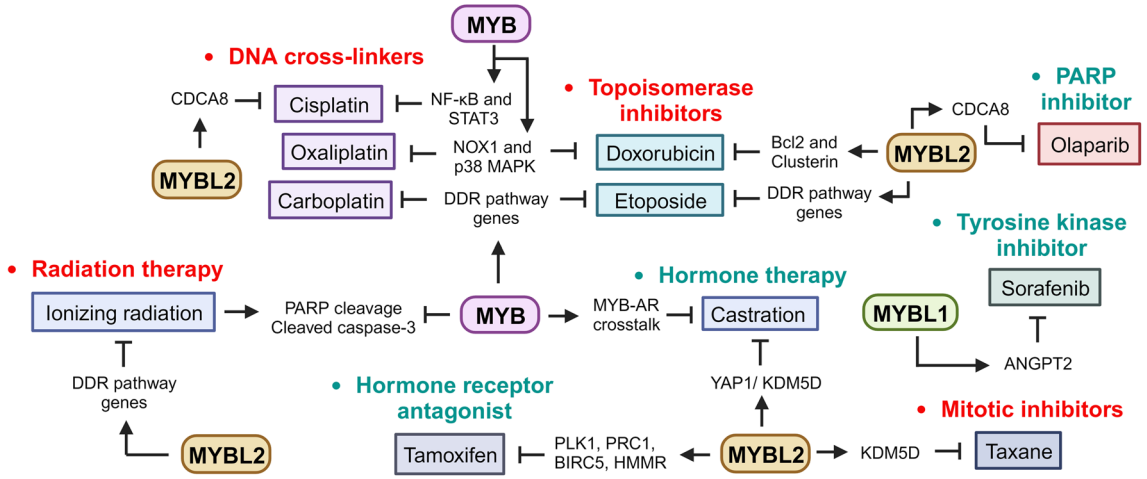

Fig. 4 Promotion of therapeutic resistance by MYB family transcription factors. MYB proteins promote resistance against both targeted (shown in cyan) and non-targeted (shown in red) therapeutic drugs. MYB promotes cisplatin resistance by increasing the expression of NFκB and STAT3, carboplatin/etoposide resistance by increasing the expression of DNA damage response (DDR) pathway-related genes, radiation therapy resistance by preventing the PARP cleavage, and oxaliplatin/doxorubicin resistance by activation of NOX1/p38MAPK pathways in different cancer types. Similarly, MYBL2 contributes to resistance against doxorubicin and tamoxifen drugs by regulating the expression of Bcl-2 and PLK1, PRC1, BIRC5, and HMMR. Development of resistance against targeted therapies including radiation therapy, castration therapy, taxane, and sorafenib drug has also been shown to be associated with activation of MYB family transcription factors

resumed the serum PSA levels [97]. In additional studies, we have observed racially disparate expression of MYB in prostate and ovarian malignancies associated with patient's prognosis and disease recurrence (unpublished data; [98]). An upregulation of B-MYB is also reported in CRPC tissues and cell lines, where it supports the resistance to androgen-deprivation therapy and taxane drugs [99]. Another study suggested that B-MYB contributed to castration-resistance by activating the YAP1 transcription [100]. Overexpression of B-MYB in T-lymphoblastic cells enhanced the expression of Bcl-2 and resistance to killing by doxorubicin, ceramide, and dexamethasone [101]. MYBL2 transcriptionally upregulates Clusterin expression, which mediates at least in part, the antiapoptotic effects of B-MYB and confer doxorubicin resistance in neuroblastoma cells [102]. It is also shown to contribute to tamoxifen resistance in breast cancer cells by upregulating genes associated with survival [103]. A pan-cancer analysis of B-MYB function using various bioinformatics approaches also predicted its role in chemoresistance and immune escape via regulation of apoptosis and immune-checkpoint-associated genes [104]. Elevated expression of MYBL2 in lung adenocarcinoma drives the expression of a set of genes that mediate replication stress response and promote error-prone DNA repair which were also coupled with loss of cell cycle check-point regulators TP53 and RB1 [105]. Moreover, MYBL2 upregulates the expression of cell division cycle associated 8 (CDCA8) protein, a component of chromosomal passenger complex (CPC) and confers olaparib and cisplatin resistance in ovarian cancer cells by regulating the apoptosis and homologous recombination-mediated DNA damage repair [106]. The information on the role of A-MYB in therapy resistance is scarce. Hepatocellular carcinoma cells expressing higher A-MYB exhibit resistance to sorafenib and its inhibition abrogates this resistance [86]. Thus, it appears that MYB family proteins are good targets for achieving the therapeutic enhancement of existing targeted or non-targeted anticancer drugs. Moreover, expression of MYB proteins could also be used as a potential biomarker for therapeutic planning and predicting the response to chemo- and immune therapies.

5 Role of MYB in stromal remodeling and its impact on tumor cell plasticity, metastasis, and therapy resistance

Tumor cells continuously interact with other cells in the tumor microenvironment (TME), such as fibroblasts, endothelial cells, and immune cells, throughout the course of cancer evolution. These dynamic interactions create a tumor-supportive environment by modifying the phenotypes and makeup of the stromal cells as well as altering the composition of the extracellular matrix [107, 108]. We have shown that MYB-overexpression in pancreatic cancer cells promotes desmoplasia by increasing the secretion of sonic hedgehog (SHH) and adrenomedullin (ADM) [109]. MYB transcriptionally upregulated SHH and ADM, which activated pancreatic stellate cells (PSC) allowing their transition

to myofibroblasts. A greater abundance of collagen-1, fibronectin, and α-Smooth muscle actin (α-SMA)-positive fibroblast cells was recorded in orthotopic xenografts derived from MYB-expressing pancreatic cancer (PC) cells than those from MYB-silenced cells [109]. This is interesting since extensive desmoplasia in pancreatic tumors has been reported to be a significant cause of chemoresistance. A seminal study by Olive et al. demonstrated that desmoplastic stroma restricted the delivery of gemcitabine to the tumor cells in a genetically engineered mouse model of pancreatic adenocarcinoma [110]. Increased desmoplasia also creates a more hypoxic environment that is known to cause EMT, promote metastasis, and reduce the efficacy of anticancer drugs in many cancers [111, 112].

High MYB expression in colorectal cancer has been associated with reduced infiltration of activated T-cells near the tumor and poor relapse-free survival. This reciprocal relationship indicatse that MYB could be useful as a marker to predict patient response to immunotherapy [113]. Further, MYB-promoted desmoplasia could also restrict immune cell infiltration and/or may be inhibitory to their proliferation and survival within the tumor microenvironment [114, 115]. In a recent study, loss of structural integrity of desmoplastic matrix promoted efficacy of tumor antigen (mesothelin)-targeted CAR-T cells and anti-PD-1 antibody therapies in solid tumors [115]. CXCL12, the ligand for chemokine receptor CXCR4 and abundantly expressed by activated tumor-associated fibroblasts, promotes fibrosis, and inhibition of CXCR4 is shown promote T-lymphocyte infiltration and induce an integrated immune response in breast, pancreatic and colorectal cancers [71, 116, 117]. Recent studies revealed that senescent fibroblasts near the tumor cells undergo changes in the expression of genes associated with cell cycle, metabolism, and secretory proteins leading to gain of a pro-inflammatory secretory phenotype [118]. The secretion of pro-tumorigenic SASP factors, such as osteopontin (OPN), IL-6, and IL-8, is regulated by MYB and promotes the growth and migration of cancer cells [119–121]. MYB expression is also upregulated in macrophages upon co-culture with the breast cancer cells. Further, it transcriptionally represses the 5-Lipoxygenase (5-LO), a key enzyme in leukotrienes biosynthesis, and leads to reduced T-cell recruitment favoring tumor progression [122]. Thus, MYB can not only affect tumor cell features through direct tumor-intrinsic actions but also by modulating the tumor microenvironment.

6 Conclusion

Identifying and characterizing the genes involved in tumorigenesis are crucial to develop novel molecular approaches for cancer management. From early reports demonstrating the expression of MYB in hematopoietic stem cells, the field has moved fast demonstrating the aberrant expression and/or activation of MYB family proteins in multiple malignancies. Further, we have learnt a great deal regarding the involvement of MYB proteins in multiple oncogenic processes, including proliferation, survival, stemness, invasion, and stromal remodeling. Also, these proteins appear to support the growth of cancer cells under harsh environmental conditions and fight therapeutic insults. More interestingly, racial differences in MYB expression are also reported suggesting its role in racially-disparate clinical outcomes. Thus, targeting MYB could be a useful strategy to effectively manage cancer and narrow the disparity gaps. Having said that, there is still a lot to learn about MYB functions in cancers. It is important to scan the complete spectrum of target genes of MYB proteins in different cancers and at different stages of cancer development. Most transcription factors work in concert with other proteins and the differential protein–protein interactions impact the transcriptional output. For example, we have found an interaction of MYB with HIF-1α, which is expressed at the protein level under an oxygen-reduced environment. Our initial data suggest that this interaction promotes metabolic reprogramming and helps the cells to switch from a proliferative state to a slow growing state, which is more invasive. This is a great example of the role of MYB in tumor cell plasticity and should be explored further in different tumor types and when the tumor cells are exposed to other environmental stressors, including therapeutic treatments. This new knowledge could be highly useful to develop approaches for therapeutic targeting of cancer-supporting MYB functions and therapeutic enhancement of existing treatment modalities. It is also important to delineate the molecular mechanisms involved in controlling the expression and activation of MYB proteins. Such an information can also provide additional therapeutic opportunities and even help in developing strategies for cancer prevention.

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Literature search, review, and writing original draft: SA, KSV, SKS, AS, SA, and MAK.

Discussion of cited literature and feedback on the manuscript draft: SS.

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