

# Association between B-Myb proto-oncogene and the development of malignant tumors (Review)

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**Abstract.** B-Myb is a critical transcription factor in regulating cell cycle. Dysregulated expression of B-Myb promotes tumor formation and development. B-Myb is a proto-oncogene ubiquitously expressed in proliferating cells, which maintains normal cell cycle progression. It participates in cell apoptosis, tumorigenesis and aging. In addition, B-Myb is overexpressed in several malignant tumors, including breast cancer, lung cancer and hepatocellular carcinoma, and is associated with tumor development. B-Myb expression is also associated with the prognosis of patients with malignant tumors. Both microRNAs and E2F family of transcription factors (E2Fs) contribute to the function of B-Myb. The present review highlights the association between B-Myb and malignant tumors, and offers a theoretical reference for the diagnosis and treatment of malignant tumors.

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## 1. Introduction

B-Myb, also known as MYB proto-oncogene like 2 (MYBL2), is a transcription factor that belongs to the Myb gene family,

including A-Myb and c-Myb (1). MYB was the first discovered family member and is the mammalian homolog of the retro-viral v-Myb oncogene that causes acute leukemia in birds and can transform hematopoietic cells (2). A-Myb is predominantly expressed in germ cells and primordial lymphocytes (3). c-Myb is highly expressed in cells of the hematopoietic system, with low expression in epithelial cells of specific tissues, such as the colon and brain (3,4). B-Myb is ubiquitously expressed in mammalian cells with high proliferative ability (1,4,5), and B-Myb is a physiological regulator of cell cycle progression, cell survival and cell differentiation (6). However, several experimental studies have demonstrated that B-Myb is highly expressed in different types of human malignant tumors, including breast cancer (7), lung cancer (8), hepatocellular carcinoma (9), endometrial cancer (10), prostate cancer (11) and ovarian cancer (12). Both *in vivo* and *in vitro* experiments have demonstrated that high B-Myb expression promotes colony formation, cell cycle progression, migration and invasion of cancer cells (13). B-Myb also participates in the occurrence of epithelial-to-mesenchymal transition (EMT) in malignant tumor, inhibits cancer cell apoptosis and results in a poor prognosis (14). However, the molecular mechanisms underlying the regulation of B-Myb in the development of malignant tumors remain unclear.

The present review highlights the association between B-Myb proto-oncogene and the development of malignant tumors based on available studies, aiming to provide insight into the molecular mechanisms underlying B-Myb-induced development of malignant tumors.

## 2. Role of B-Myb in the development of malignant tumors

**B-Myb expression in malignant tumors.** B-Myb is expressed at high levels in several human malignant tumor tissues (Table I). For example, there are five molecular subtypes of breast cancer, basal-like, human epidermal growth factor receptor 2 positive (HER2+)/estrogen receptor negative (ER-), luminal A, luminal B and normal-like (7). Microarray analyses of B-Myb in breast cancer tissues have demonstrated that its expression levels significantly differ among the five subtypes, with the highest level in basal-like tumors (7). Furthermore, overexpression of B-Myb has been observed in 83% of primary tumors

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and all cell lines of non-small cell lung cancer (NSCLC) (8), and B-Myb has also been demonstrated to modulate cell cycle and proliferation (15). Frau *et al* (9) assessed B-Myb mRNA and protein expression levels across different stages of hepatocarcinogenesis and demonstrated that B-Myb expression levels were substantially higher in precancerous lesions, early proliferative nodules, advanced proliferative nodules and hepatocellular carcinoma compared with normal liver tissues. In addition, the highest levels of B-Myb were observed in hepatocellular carcinoma, among the four different stages. Nakajima *et al* (16) reported amplification of the B-Myb gene copy number in 36/66 cases of primary hepatocellular carcinoma.

In the absence of gene amplification, malignant tumors of the prostate exhibit elevated B-Myb expression levels, and B-Myb expression is markedly higher in metastatic prostate cancer compared with non-metastatic prostate cancer (11,17). Based on a study involving 180 patients with colorectal cancer, B-Myb mRNA and protein expression levels were notably higher in cancer tissues compared with adjacent normal tissues, and B-Myb expression was positively associated with tumor size and clinical stage (18).

Qin *et al* (19) demonstrated that B-Myb is amplified in esophageal cancer, based on whole-genome sequencing (10 pairs) and whole-exome sequencing (57 pairs) of esophageal cancer tissues and matched adjacent normal tissues selected from high-incidence areas of esophageal cancer in China. Additionally, Qin *et al* (20) reported that B-Myb protein was expressed at higher levels in esophageal squamous cell carcinoma (ESCC) tissues compared with adjacent normal tissues in a Chinese population of 107 patients with ESCC, based on immunohistochemistry.

Among patients with neuroblastoma, individuals with malignant metastasis and poor prognosis express B-Myb at significantly elevated levels; this phenomenon suggests that B-Myb expression is associated with the risk of developing neuroblastoma (21). Notable, inhibition of B-Myb expression prevents the proliferation of normal human cells and cancer cells (21-24). In addition, B-Myb expression levels are significantly higher in glioma tissues compared with adjacent normal tissues and are positively associated with the grade of glioma, based on the results of reverse transcription-PCR (RT-PCR) and western blot analyses from 79 patients with glioma (25).

In renal cell carcinoma, metastatic tumor tissues highly express B-Myb when metastasis occurs in primary tumors negative for B-Myb expression (26). B-Myb is also amplified in high-grade bladder cancer (27). In addition, high B-Myb expression has been implicated in leukemias (28), gallbladder cancer (29), fibrosarcoma (30), ovarian cancer (12) and aggressive T-cell lymphoma (31).

### 3. Biological function of B-Myb in malignant tumor development

**Promotion of cancer cell proliferation.** Increasing evidence suggests that B-Myb is overexpressed in different types of human cancer, including breast cancer (32), cervical cancer (33), colorectal cancer (18), liver cancer (34), leukemia cells (28) and lung cancer (35). In these types of cancer, B-Myb promotes cell proliferation and/or cell cycle

progression (18,34). Thomas *et al* (36) observed a positive correlation between B-Myb mRNA expression and Ki-67 proliferation index in breast cancer. In addition, the breast cancer cell line, MDA-MB-231, exhibits remarkably decreased abilities to form colonies, migrate and invade following knock-down of B-Myb with short-hairpin RNA (37). Flow cytometric analysis demonstrated that the cell cycle is arrested at S and G<sub>2</sub>/M phases, while *in vivo* experiments indicated that both the rate of tumor formation and the weight of tumor mass are significantly lower in breast cancer compared with the control group (32).

Jin *et al* (13) demonstrated that overexpression of B-Myb promotes the proliferation of NSCLC cells; both extracellular regulated MAP kinase (ERK) and phosphorylated-protein kinase B (Akt) signaling pathways participate in the modulation of NSCLC by B-Myb. Liang *et al* (29) reported that B-Myb expression is upregulated in gallbladder cancer tissues, which in turn facilitates the proliferation of gallbladder cancer cells by facilitating cell cycle progression through the S and G<sub>2</sub>/M phases (30).

In ESCC, an EdU-retention assay demonstrated that downregulation of B-Myb expression decreases the DNA synthesis ability of EC9706 cells, while a Cell Counting Kit-8 assay demonstrated that overexpression of B-Myb also promotes the proliferation of KYSE510 cells (20). These findings suggest that B-Myb can promote the proliferation and DNA synthesis of ESCC cells. Based on a colony formation assay, overexpression of B-Myb in the low-grade glioma cell line, Hs683, considerably increased the number of colonies, whereas knockout of B-Myb in the high-grade glioma cell line, U251, decreased the number of colonies (25). Subsequently, a MTT assay demonstrated that the proliferative ability of glioma U251 cells is enhanced following transfection with small interfering (si)RNAs (25).

**Promotion of EMT.** B-Myb has been demonstrated to play a role in EMT, a process whereby epithelial cells lose their polarity, migrate and increase polarity (38). In breast cancer cells, downregulation of B-Myb expression can recover the expression of the epithelial marker, E-cadherin and promote the formation of intercellular adhesion, in addition to inhibiting cell invasion, anchorage-dependent growth and tumor formation (32). Conversely, overexpression of B-Myb can decrease E-cadherin expression and increase the expression of mesenchymal markers (14). In addition, it has been demonstrated that B-Myb can upregulate the expression of Snail, a key regulator of EMT, thereby mediating the promotion of EMT and cancer cell invasion (14).

The role of B-Myb in colorectal cancer invasion and metastasis has also been proven and is associated with EMT (18). For example, EMT inhibits B-Myb activity in colorectal cancer cells, thereby upregulating the expression of the epithelial marker, E-cadherin and downregulating the expression of the mesenchymal marker, Vimentin and matrix metalloproteinase 9 (MMP9) (18). Based on a western blot assay on the expression of EMT markers in glioma cells, interference with B-Myb expression inhibits the protein expression levels of N-cadherin, Vimentin, MMP2 and MMP9, while upregulating the protein levels of E-cadherin and zinc finger E-box binding homeobox 1 (25). Taken together, these findings suggest that

Table I. Role of B-Myb in malignant tumor development.

Tumor type	B-Myb expression level	Patient prognosis	B-Myb expression treatment	<i>In vitro</i> effect on cell phenotype	<i>In vivo</i> effect on nude mice	(Refs.)
Breast cancer	High	Poor	Interference	Inhibit cell cycle progression, cell proliferation, and cell migration and invasion.	Inhibit tumor formation.	(7,32)
Lung cancer	High	Poor	Overexpression	Promote tumorigenesis, cell proliferation and cell cycle progression.	Promote tumor formation.	(8,13,78)
			Interference	Inhibit cell proliferation, cell cycle progression, and cell migration and invasion.	Inhibit tumor formation.	
Hepatocellular carcinoma	High	Poor	Overexpression	Promote tumorigenesis, cell proliferation and cell cycle progression.	-	(9,34)
			Interference	Inhibit cell proliferation and cell cycle progression.	-	
Colorectal cancer	High	Poor	Interference	Inhibit cell proliferation, cell cycle progression and cell migration and invasion.	-	(18)
Esophageal squamous-cell carcinoma	High	Poor	Overexpression	Promote cell cycle progression and cell proliferation.	-	(19,20)
			Interference	Inhibit cell proliferation.	Inhibit tumor formation.	
Gallbladder cancer	High	Poor	Overexpression	Promote cell cycle progression and cell proliferation.	Promote tumor formation.	(29)
			Interference	Inhibit cell cycle progression and cell proliferation.	Inhibit tumor formation.	
Glioma	High	Poor	Overexpression	Promote cell proliferation.		(25)
			Interference	Inhibit cell cycle progression and cell proliferation.		
Prostate cancer	High	-	-	-	-	(11,17)
Renal cell carcinoma	High	-	-	-	-	(26)
Ovarian cancer	High	-	-	-	-	(12,31)
Neuroblastoma	High	Poor	-	-	-	(47)
Fibrosarcoma	High					(30)
Endometrial cancer	High	-	-	-	-	(10)
Primary leukemia	High	-	-	-	-	(28)

-, not available.

B-Myb plays an important role in the promotion of EMT in several malignant tumors, thereby facilitating cancer cell infiltration and metastasis.

**Inhibition of cancer cell apoptosis.** B-Myb inhibits cancer cell apoptosis potentially through multiple pathways. First, B-Myb may perform its anti-apoptotic function by positively regulating the expression of the anti-apoptotic gene, Clusterin (30), also known as apolipoprotein J (39). A study demonstrated that inhibition of Clusterin gene expression promotes the apoptosis of fibrosarcoma cells (30). Secondly, B-Myb may inhibit apoptosis by positively regulating the expression

of the anti-apoptotic gene, *Bcl-2* (40), a critical regulator of apoptosis (41). In support of these pathways, the anti-apoptotic function of B-Myb has been observed in different cancer cell lines, including colorectal cancer (18) and liver cancer (34).

Ren *et al* (18) reported that Bcl-2 protein expression is downregulated in SW480 colorectal cancer cells via interference with B-Myb expression. Calvisi *et al* (34) demonstrated that B-Myb exerts an anti-apoptotic function, and interference with B-Myb expression via transfection with siRNA induces apoptosis in four different hepatocellular carcinoma cell lines. In glioma U251 cells transfected with B-Myb siRNA, Zhang *et al* (25) detected an increase in the percentage of

apoptotic cells by Annexin V-FITC/PI and hoechst 3342 staining. Furthermore, Zhang *et al* (25) assessed the effects of B-Myb silencing on apoptosis-related proteins, including caspase-3/9, Bcl/Bax, PTEN and P53. Western blot analysis demonstrated that B-Myb silencing decreases Bcl-2 expression, while increasing the expression levels of Bax, PTEN and P53, and activates caspase-3/9 activity. Taken together, these results suggest that downregulation of B-Myb can induce apoptosis in glioma cells.

**Enhancement of drug resistance.** The role of B-Myb in tumor resistance to therapy is associated with its pro-apoptotic function (42,43). Overexpression of B-Myb promotes the expression of the anti-apoptotic gene, *Bcl-2* in IL2-dependent murine CTLL-2 cells, thereby increasing the therapeutic resistance to drugs, including doxorubicin, ceramide and dexamethasone (42). Similarly, Levenson *et al* (43) demonstrated that B-Myb expression is notably upregulated in fibrosarcoma cells with therapeutic resistance induced by chemotherapeutic drugs that inhibit DNA synthesis, including hydroxyurea, cysteine, etoposide and adriamycin. Furthermore, B-Myb regulates the expression of the anti-apoptotic gene, Apolipoprotein J/Clusterin in neuroblastoma cells to resist apoptosis caused by doxycycline (30).

Sottile *et al* (44) reported that individuals with B-Myb overexpression or *MYCN* amplification are more sensitive to therapy with camptothecins (irinotecan and topotecan) among patients with neuroblastoma. B-Myb is a downstream target of *MYCN*; *MYCN* amplification promotes B-Myb overexpression, while B-Myb overexpression in turn promotes an upregulation of *MYCN* expression, thus these two factors regulate each other (21). Camptothecins selectively downregulate B-Myb and *MYCN* expression, while upregulation of B-Myb decreases the killing effect of camptothecins, suggesting that B-Myb is an important target of camptothecins (44). In addition, B-Myb is overexpressed in cetuximab-resistant NSCLC, suggesting that B-Myb overexpression is associated with cetuximab resistance (45).

**Effect on patient prognosis.** High B-Myb expression is associated with tumor growth and poor prognosis of patients, making it a potential clinical marker for poor prognosis (20,46). Based on microRNA (miRNA/miR) prediction and RT-PCR analyses, B-Myb may have a negative regulatory association with miR-30 family members, and biochemical relapse-free survival time is shortened in patients with acute myeloid leukemia highly overexpressing B-Myb; thus, B-Myb can be a predictive marker for the prognosis of patients with acute myeloid leukemia (46). In addition, B-Myb expression is elevated in ESCC tissues and negatively associated with post-operative overall survival in patients with ESCC, as revealed by a Kaplan-Meier analysis (20).

A prognostic analysis of breast cancer and its different subtypes revealed that the B-Myb high expression group has a worse prognosis compared with the low expression group (7). High B-Myb expression also increases the risk of poor prognosis, decreases the differentiation ability of cells, and promotes tumor development in neuroblastoma (47). In HepG2 and HuH7 hepatocellular carcinoma cell lines, overexpression of B-Myb increases the cell proliferative ability and

facilitates G<sub>1</sub>-S and G<sub>2</sub>-M transitions, whereas interference of B-Myb with siRNA results in cell cycle arrest at G<sub>0</sub>-G<sub>1</sub> and G<sub>2</sub>-M phases (9).

Among patients with colorectal cancer, the 5-year survival rate is notably lower in individuals with high B-Myb expression than those with low B-Myb expression; B-Myb expression and clinical stage of the tumor can be used as independent prognostic factors of colorectal cancer (18). With regards to the prognosis and survival of 79 patients with glioma, Kaplan-Meier analysis and log-rank test results indicated that high B-Myb expression is negatively associated with survival, and is a poor prognostic factor in patients with glioma (25).

**Role of B-Myb in the diagnosis and treatment of malignant tumors effect.** B-Myb plays a role in the clinical diagnosis and treatment of malignant tumors. B-Myb can be used as a biological marker of cervical cancer to make up for the limitations of conventional cytology for cervical intraepithelial neoplasia and cervical cancer diagnosis in routine cervical cytology testing (43,44). Astbury *et al* (48) measured MYBL2 expression levels in cervical cancer cell lines, cervical intraepithelial neoplasia and cervical glandular epithelium using genomics and proteomics technology, and assessed the potential of B-Myb as a biomarker. Previous studies (47) have demonstrated that patients with neuroblastoma, with MYBL2 overexpression, are more sensitive to camptothecin therapy (44). Camptothecin drugs can selectively downregulate the expression of B-Myb. Conversely, upregulating B-Myb can decrease the killing effect of camptothecin drugs (44). Collectively, these results suggest that B-Myb is an important target of camptothecin drugs (44).

#### 4. Regulatory mechanisms of B-Myb in malignant tumor

**B-Myb regulation by miRNAs.** miRNAs are a group of small non-coding single stranded RNAs that have been extensively observed in animals and plants, typically 18-22 nucleotides in length (49). Both misregulation and mutation of miRNAs can cause tumorigenesis, and they contribute to the function of oncogenes through targeted downregulation of tumor suppressor genes or activation of oncogene transcription factors (50,51). B-Myb is mainly regulated by the miR-29 and miR-30 families (52). In breast cancer cell lines, miRNA binds to the 3'-untranslated region of B-Myb and thereby inhibits B-Myb expression (53). Additionally, miR-29a expression is negatively correlated with B-Myb expression, and *cyclin A2* and *cyclin D1* expression is positively correlated with B-Myb expression (54). These results indicate that miR-29a suppresses tumor growth by downregulating B-Myb expression (54).

Geng *et al* (55) reported that miR-30a expression is significantly downregulated in NSCLC tissues compared with adjacent normal tissues, and B-Myb is a target gene of miR-30a based on a double-luciferase reporter gene assay; miR-30a can suppress proliferation and growth of NSCLC through targeted inhibition of B-Myb expression. Li *et al* (56) demonstrated a close association between B-Myb overexpression and low levels of miR-30a, miR-30b and miR-30c in 291 patients with acute myeloid, based on RT-qPCR analysis of B-Myb, miR-29 family and miR-30 family genes. Li *et al* (56) reported that the long non-coding RNA, LINC01139, upregulates B-Myb by

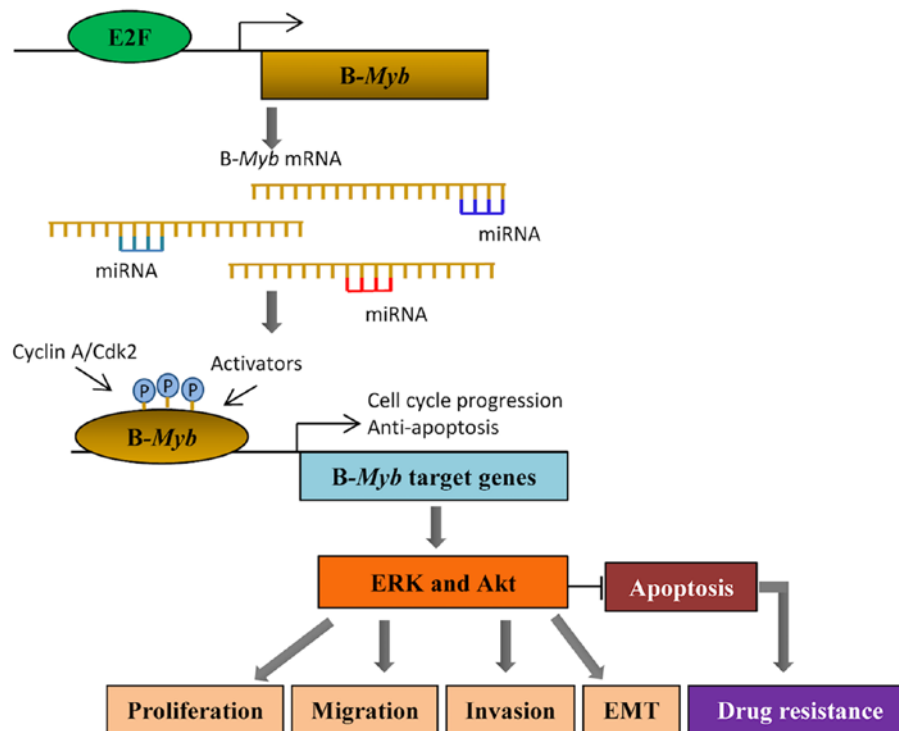


Figure 1. Schematic diagram depicting the association between B-Myb proto-oncogene and the development of malignant tumors. miRNA, microRNA; Cdk2, cyclin-dependent kinase 2; EMT, epithelial-to-mesenchymal transition; E2F, transcription factor E2F; ERK, extracellular signal-regulated kinases; Akt, phosphorylated-protein kinase B.

competitively binding to the miR-30 family, thereby promoting the progression of hepatocellular carcinoma.

B-Myb is also regulated by other miRNAs during tumor development. Zauli *et al* (28) demonstrated that the cell cycle is arrested at G<sub>1</sub> following downregulation of B-Myb expression in primary leukemia cells and P53 wild-type myeloid and lymphoblastic cells; miR-34a plays a pivotal regulatory role in this process. Lee *et al* (57) reported that inhibition of miR-34a recovers B-Myb expression, while miR-34a mimics downregulates B-Myb expression in HCT116 colorectal cancer cells. In addition, Li *et al* (56) and Yu *et al* (58) have concluded that the expression of G<sub>1</sub>/S-related genes, *Ezh2* and B-Myb, are suppressed by miR-34c overexpression in the cancer cell line cultured from a mouse model of tubal high-grade serous ovarian carcinoma, leading to cell cycle arrest at G<sub>1</sub> phase and induction of apoptosis.

Wang *et al* (59) demonstrated that post-transcriptional regulation of *MALAT1* is regulated by miR-101 and miR-217 in ESCC. Specifically, post-transcriptional silencing of *MALAT1* significantly inhibits ESCC cell proliferation by arresting the G<sub>2</sub>/M phase, while the migratory and invasive abilities of ESCC cells decrease following overexpression of miR-101 and miR-217. This may be due to *MALAT1*-mediated upregulation of *P21* and *P27* expression and inhibition of B-Myb expression (60). In addition, Chen *et al* (61) indicated that miR-143-3p negatively regulates B-Myb in breast cancer cells, and modulates cancer cell proliferation and apoptosis (62).

**B-Myb regulation by E2Fs.** The E2F transcription factor family plays a crucial role in the regulation of cell cycle progression, DNA replication and apoptosis (63). The E2F family can be divided into two groups, *E2F1-3a* are transcription factors that activate the cell cycle and mainly encode genes that promote the

progression of G<sub>1</sub> to S phase, while *E2F3b* and *E2F4-8* mainly promote cells to exit the cell replication cycle and facilitate cell differentiation (64,65). B-Myb is a typical cell cycle regulator that is rarely expressed in the G<sub>0</sub> phase (66). When external growth factor-mediated signal pathways, such as ERK1/2, are activated, they promote the release and activation of *E2F1-3* from pRB through *CCND1*; these factors drive their target genes to encode G<sub>1</sub>/S-related cytokines, and B-Myb expression is also induced by *E2F1-3* (4,67,68). The induction of B-Myb expression at the end of the G<sub>1</sub> phase is due to a substantial increase in gene transcription, suggesting that B-Myb may be a gene regulated by the E2F transcription factors (62).

The promoters of both human and murine B-Myb genes contain completely conserved E2F-binding sites, which is key for B-Myb to participate in the transcription regulation of the cell cycle (69,70). A chromatin immunoprecipitation assay of NIH3T3 in fibroblasts revealed that both *E2F4/P107* and *E2F4/P130* are associated with the B-Myb promoter in the G<sub>0</sub> phase, while *E2F4/P107* is associated with the B-Myb promoter in the early G<sub>1</sub> phase (69). In human malignant glioma T98G cells, *E2F1* and *E2F3* are associated with the B-Myb promoter in the late G<sub>1</sub> phase (71). B-Myb transcriptionally activates its own promoter through the *SPI*-binding site adjacent to the transcription initiation site (72). *SPI* is coupled with *E2F1* to promote transcriptional activation of the B-Myb promoter (73,74). It is suggested that *E2F1* and *E2F3* play a role in promoting B-Myb transcription in at least some cells (75).

Nakajima *et al* (16) demonstrated that knockout of *E2F1* in JHH-5 hepatocellular carcinoma cells decreases the expression levels of B-MYB, *CCNE1*, *MYC*, *TK1* and *RRM1*. The kinetics of B-Myb interaction with G<sub>2</sub>-regulated promoters coincides with the activation of the genes; a decrease in RNAi-regulated

B-Myb expression can inhibit *cyclin B1* and cell division cycle 2 (*cdc2*) expression, arrest cell cycle at G<sub>2</sub>/M, and increase apoptosis (76). The interaction of B-Myb with the *cdc2* promoter is dependent on the complete *E2F*-binding site, and the B-Myb gene is regulated by *E2F* at G<sub>1</sub>/S transition, thereby modulating the target genes associated with G<sub>1</sub>/S and G<sub>2</sub>/M transitions, including *cdc2*, *cyclin A2* and *cyclin B1* (77).

## 5. Conclusions

B-Myb, a classic oncogene, promotes the development of malignant tumors (5). B-Myb is highly expressed in several tumors, and its expression is associated with the clinicopathological characteristics of tumors (13,33,78). High B-Myb expression severely affects the prognosis of patients, with a relatively low 5-year survival rate (7). *In vitro* studies have demonstrated that B-Myb promotes cell cycle progression, proliferation, invasion and migration of cancer cells (35). *In vivo* experiments have also reported that B-Myb facilitates tumor formation (35). Both miRNAs (46,47,51) and *E2Fs* (16) contribute to the function of B-Myb by regulating its expression. miR-29, miR-30, miR-34, amiR-101 and miR-217 all participate in the regulation of B-Myb, thus affecting cell functions, including senescence, proliferation, invasion and metastasis (Fig. 1). *E2Fs* interact with B-Myb through promoter elements, which in turn activates target genes involved in G<sub>1</sub>/S and G<sub>2</sub>/M transitions, thereby promoting cell cycle progression (16). Following research advances on the molecular mechanisms of malignant tumor development, it may be possible to apply B-Myb to the diagnosis and treatment of patients with tumors. Determining the role of B-Myb in tumor development will provide novel tumor markers, while starting a novel chapter of potential targeted intervention therapy of malignant tumors.

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## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Authors' contributions

YJ, GQ, GC, CW and XF made substantial contributions to conception and design, or acquisition of data, or analysis and

interpretation of data. XF and YJ drafted the initial manuscript and critically revised it for important intellectual content. GC and CW designed the study, and critically revised the article. XF approved the final version to be published.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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