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.

Contents

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 retroviral 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 knockdown of B-*Myb* with short-hairpin RNA (37). Flow cytometric analysis demonstrated that the cell cycle is arrested at S and G_2/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_2/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	*In vitro* effect on cell phenotype	*In vivo* 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 hochest 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 downregulates 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 postoperative 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_1-S and G_2-M transitions, whereas interference of B-*Myb* with siRNA results in cell cycle arrest at G_0-G_1 and G_2-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

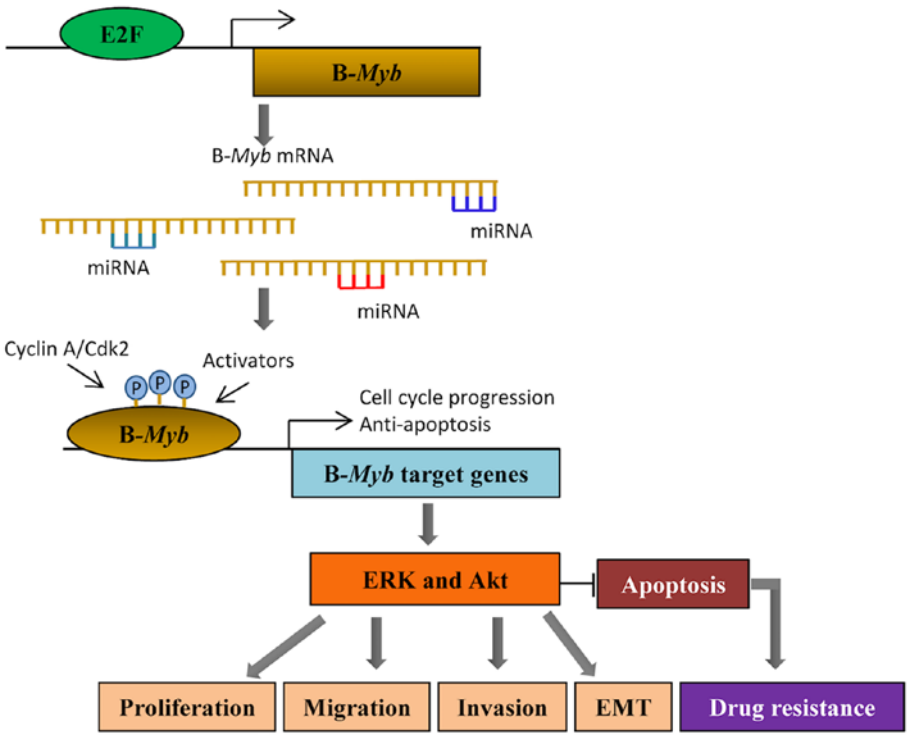

Figure 1. Schematic diagram depicting the assoication between B-*Myb* proto-oncogene and the development of malignant tumors. miRNA, microRNA; Cdk2, cyclin-dependent kinase 2; EMT, epithelial-to-mesenchymal transition; E2F, transcription factor E2F; ERK, extracellular signal-regulated kinases; Akt, phosphorylated-protein 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_1 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_1/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_1 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_2/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_1 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_0 phase (66). When external growth factor-mediated signal pathways, such as ERK1/2, are activated, they promotes the release and activation of *E2F1-3* from pRB through *CCND1*; these factors drive their target genes to encode G_1/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_1 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_0 phase, while *E2F4/P107* is associated with the B-*Myb* promoter in the early G_1 phase (69). In human malignant glioma T98G cells, *E2F1* and *E2F3* are associated with the B-*Myb* promoter in the late G_1 phase (71). B-*Myb* transcriptionally activates its own promoter through the *SP1*-binding site adjacent to the transcription initiation site (72). *SP1* 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_2-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_2/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_1/S transition, thereby modulating the target genes associated with G_1/S and G_2/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_1/S and G_2/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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