

Regulation of gene transcription of B lymphoma Mo-MLV insertion region 1 homolog (Review)

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Abstract. B lymphoma Mo-MLV insertion region 1 homolog (Bmi-1) is a core protein component of the polycomb repressive complex 1 that inhibits cell senescence and maintains the self-renewal ability of stem cells via down-regulation of *p16Ink4a* and *p19Arf* expression. Bmi-1 serves an important role in hematopoietic stem cell maintenance and neurodevelopment during embryonic development, and it has been shown to enhance tumorigenesis by promoting cancer stem cell self-renewal and epithelial to mesenchymal transition. Emerging evidence suggests that *Bmi-1* overexpression is closely related to the development and progression of various types of cancer, and that downregulation of Bmi-1 expression can inhibit the proliferation, invasion and metastasis of cancer cells. It is therefore important to elucidate the mechanisms underlying the regulation of Bmi-1 expression both under normal growth conditions and in malignant tissues. In the present review, the current body of knowledge pertaining to the transcriptional and post-transcriptional regulation of the *BMI-1* gene is discussed, and the potential mechanisms by which Bmi-1 is dysregulated in various types of cancer are highlighted. Bmi-1 expression is primarily controlled via transcriptional regulation, and is regulated by the transcrip-

tion <https://www.ushuaia.pl/hyphen/?ln=en> factors of the Myc family, including Myb, Twist1, SALL4 and E2F-1. Post-transcriptionally, regulation of Bmi-1 expression is inhibited by several microRNAs and certain small-molecule drugs. Thus, regulatory transcriptional factors are potential therapeutic targets to reduce Bmi-1 expression in cancer cells. Thus, the present review provides an up-to-date review on the regulation of *BMI-1* gene expression at the transcriptional and post-transcriptional level.

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1. Introduction

The polycomb group (PcG) is a class of highly conserved transcriptional repressors. They are divided into two core protein complexes: Polycomb repressive complex (PRC)1 and PRC2. Both PRC1 and PRC2 serve an important role in the maintenance of the inhibition state of chromatin by polycomb proteins. PRC2 binds to the target gene during the initial stage of transcription and recruits the PRC1 complex to bind to the target gene, which maintains the repressed state of the gene (1).

The PRC1 complex core proteins include RING1B (also referred to as RNF2), RING1A (also referred to as RING1), B lymphoma Mo-MLV insertion region 1 homolog (Bmi-1), EDR1 (also referred to as HPH1) and CBX4 (also referred to as HPC2). Among these components, Bmi-1 serves a pivotal role in the PRC1 complex (1). The binding of Bmi-1 to chromatin along with other PcG proteins of the PRC1 complex leads to histone H3K27 methylation, which results in continued silencing of the *Ink4a/Arf* locus. Decreased levels of *p16Ink4a* and *p19Arf* lead to activation of nuclear E2F and downregulation of p53 (2), which in turn promotes cell proliferation and self-renewal of cancer stem cells (Fig. 1). In addition, Bmi-1 inhibits the expression of E-cadherin by interacting with epithelial to mesenchymal transition (EMT) regulatory

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Abbreviations: PcG, polycomb group; Bmi-1, B lymphoma Mo-MLV insertion region 1 homolog; PRC, polycomb repressive complex; E2F, E2 promoter binding factor; EMT, epithelial to mesenchymal transition, SALL4, Sal-like protein 4; NLS, nuclear localization signal; PEST, a peptide sequence that is rich in proline (P), glutamic acid (E), serine (S), and threonine (T); IKK α , I κ B kinase α ; GLI, glioma-associated oncogene; KLF4, Krüppel-like factor 4; HDACi, histone deacetylase inhibitors; miRNAs, microRNAs; UTR, untranslated region

Key words: BMI-1, polycomb repressive complex, gene transcription, microRNA, transcriptional regulation, post-transcriptional regulation

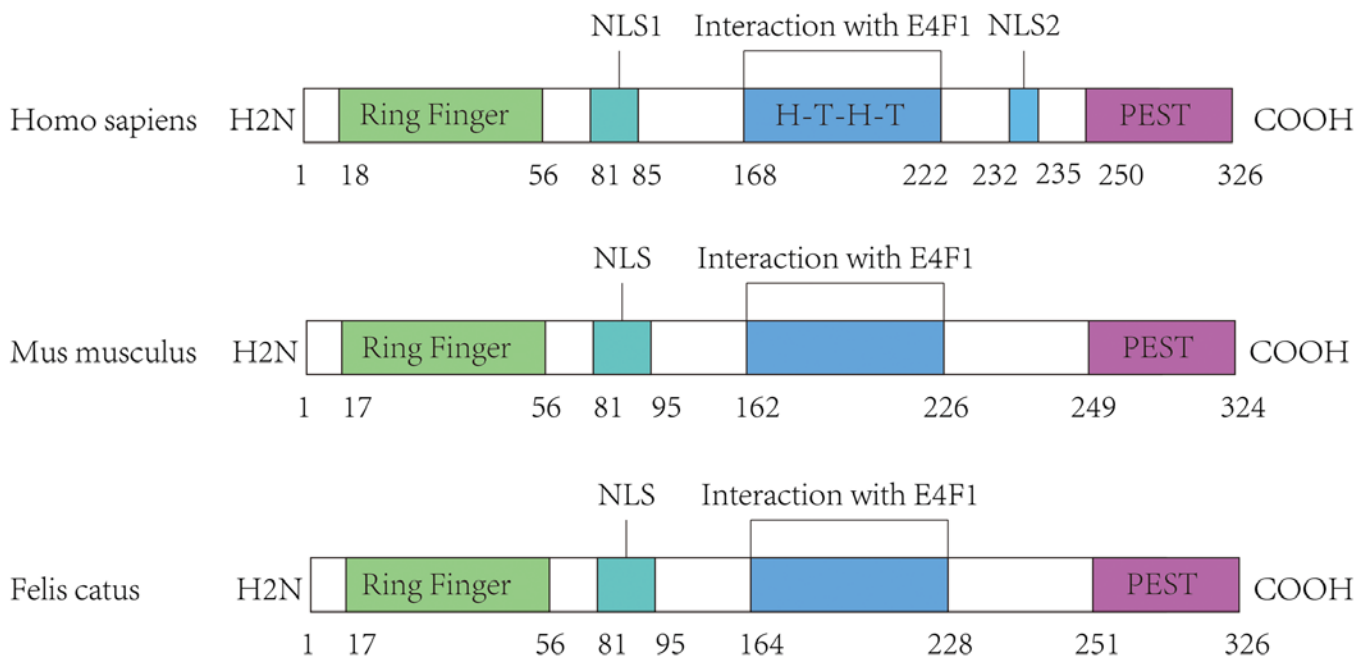


Figure 1. Function of Bmi-1. The PRC1 complex core proteins include RING1B (RNF2), RING1A (RING1), Bmi-1, EDR1 (HPH1) and CBX4 (HPC2). The binding of Bmi-1 to chromatin along with other PcG proteins of the PRC1 complex results in continued silencing of the *Ink4a/Arf* locus. Decreased levels of *p16Ink4a* and *p19Arf* lead to activation of nuclear E2F and downregulation of p53, which in turn promotes cell proliferation and self-renewal of cancer stem cells, and inhibit apoptosis. Bmi-1, B lymphoma Mo-MLV insertion region 1 homolog; PRC, polycomb repressive complex; E2F, E2 promoter binding factor; ROS, reactive oxygen species; Rb, retinoblastoma protein.

molecules, such as Twist1, Wnt, Snail and β -catenin to induce EMT, whereas inhibition of Bmi-1 expression leads to EMT reversal and decreased cell migratory ability (3). *BMI-1* is a highly conserved gene with rare mutations. It serves as a central node of various oncogenes and plays an important role in cell proliferation and tumorigenesis. Multiple signaling pathways, including N-Myc (*MYCN*), c-Myc, (*MYC*) (4), twist (3), Akt (5), and MAPK upregulate *BMI-1* expression. Under normal growth conditions, *BMI-1* expression is maintained within physiological levels through a feed-back loop that involves the PcG family members, PRC1 and PRC2 (6). However, *BMI-1* expression is upregulated in malignant cells, partly due to stimulation by oncogenes, such as *E2F-1* and *c-MYC*, and this allows for the maintenance of an undifferentiated state of the cells. *BMI-1* overexpression is a biomarker of malignant tumors and is closely related to tumor malignancy, invasion, metastasis and prognosis (7). Therefore, inhibition of *BMI-1* expression, restoration of *p16Ink4a* and *p19Arf* levels, and induction of cellular senescence are novel potential therapeutic targets for anti-cancer targeted therapy (8).

Bmi-1 is a short-lived protein, and its expression levels are controlled by various mechanisms. Bmi-1 expression is primarily controlled by transcriptional and post-transcriptional regulation (1,8). Transcriptional regulation of eukaryotic genes involves DNA methylation, histone modification, chromatin remodeling and transcription factors. Post-transcriptional regulation is predominantly achieved through regulation of RNA, which includes RNA processing and maturation, RNA transport and subcellular localization, mRNA translation and mRNA degradation (9). In this review, the recent advances in the understanding of transcriptional (Table I) and post-transcriptional regulation (Table II) of *BMI-1* expression are summarized.

2. Bmi-1 protein structure

The *BMI-1* gene was identified as a common provirus-binding site during induction of B cell lymphoma using Moroni's murine leukemia virus in transgenic mice (10). The human *BMI-1* gene is very similar to its mouse homolog and is located in the short arm 13 region of chromosome 10 (10p13). The cDNA length of human *BMI-1* gene is 3,203 bp with 86% similarity with the mouse gene sequence. The human *BMI-1* gene consists of 10 exons, which encode a protein containing 326 amino acids with 98% amino acid sequence homology with mouse Bmi-1 (11). Bmi-1 protein structure is divided into the amino terminus, the central region and the carboxyl terminus (Fig. 2). The amino terminus has a Ring Finger domain consisting of a cysteine-rich zinc finger motif and C3HC4 (12). The central region is a conserved helix-turn-helix-turn-helix-turn (HTHTHT) domain; the carboxyl terminus is considered a peptide sequence that is rich in proline (P), glutamic acid (E), serine (S), and threonine (T) (PEST) sequence. The nuclear localization signal sequence (NLS)1 (KRRR) and NLS2 (KRMK) are both located between the three regions (13). Each region has a different function, and the function of the loop finger domain is to bind to DNA and exert transcriptional regulation (14), which is also required for the activation of E3 ubiquitin ligase activity (15). The HTHTHT domain is the key structure involved in the gene transcriptional repressor function of Bmi-1 (14); the NLS consists of a short-chain amino acids that is involved in the nuclear localization of the Bmi-1 protein. The carboxy-terminal PEST region is enriched with proline, glutamic acid, serine and threonine, and is involved in the rapid intracellular degradation of Bmi-1 (16).

Table I. Factors that regulate *BMI-1* expression at the transcriptional level.

Factors	Function	(Refs.)
c-Myc	Increases Bmi-1 expression by binding to the E-box sequence in the <i>BMI-1</i> promoter	(18,19)
N-Myc	Increases Bmi-1 expression by binding to the E-box sequence in the <i>BMI-1</i> promoter	(22,23)
c-Myb	Increases Bmi-1 expression by binding 5'-flanking region nucleotides +3 to +8	(31)
Twist1	Increases Bmi-1 expression by binding the E-box sequence in intron 1 of <i>BMI-1</i> gene	(3)
SALL4	Binds to the -450 to -1 region of the <i>BMI-1</i> promoter and increases <i>Bmi-1</i> transcription	(36)
E2F-1	Combines with the E2F-1 binding site in <i>BMI-1</i> promoter to increase <i>BMI-1</i> transcriptional activity	(38,40)
Hedgehog signal	Hedgehog downstream protein GLI1 binds to <i>BMI-1</i> promoter and increases Bmi-1 transcription	(44)
FoxM1c	Promotes Bmi-1 expression by increasing c-Myc expression	(28)
Estrogen receptor α	Interacts with the <i>BMI-1</i> promoter upstream element at -327 to -172 bp to activate <i>BMI-1</i> transcription	(45)
Sp1	Binds to the region from +181 to +214 within the <i>BMI-1</i> promoter and increases <i>BMI-1</i> transcriptional activity	(46)
Nrf2	Promotes <i>BMI-1</i> transcription via an unknown mechanism	(49)
Id1	Promotes Bmi-1 expression by increasing c-Myc expression	(49)
Mel-18	Suppresses Bmi-1 expression via inhibition of c-Myc expression	(20,26)
HDACi	Indirectly inhibits <i>BMI-1</i> promoter activity	(50)
KLF4	Binds to the <i>BMI-1</i> promoter sequence, -233 to 0, to suppress <i>BMI-1</i> transcription	(47)
Copper sulfate	Inhibits Bmi-1 expression via an unknown mechanism	(70)

Bmi-1, B lymphoma Mo-MLV insertion region 1 homolog; E2F, E2 promoter binding factor; SALL4, Sal-like protein 4; Id1, inhibitor of differentiation and DNA binding; HDACi, histone deacetylase inhibitor; KLF4, Krüppel-like factor 4.

Table II. Factors that regulate *BMI-1* expression at the post-transcriptional level.

Factors	Cell or tissue types	(Refs.)
miR-15a	Gastric tumor tissues	(58)
	Prostate tumor tissues	(71)
miR-16	Ovarian cancer tissues	(53,66)
miR-30d	Prostate cancer	(61)
miR-30e*	Tumor-associated macrophages in gastrointestinal cancer	(61)
miR-34a	Brain tumor; breast cancer	(54,72)
miR-128	Brain tumor	(54)
miR-135a	Pancreatic ductal adenocarcinoma	(56)
miR-141	Human diploid fibroblasts	(60)
miR-183	Gastric cancer	(57)
miR-194	Endometrial cancer cell lines	(59)
miR-200b	Prostate cancer	(62)
miR-200c	Melanoma	(65)
miR-203	Leukemia stem cells	(63)
miR-218	Colon cancer	(55)
miR-221	prostate cancer	(71)
miR-302	MCF7, HepG2 Cell lines	(73)
miR-320a	Nasopharyngeal carcinoma.	(60)
miR-452	Colorectal cancer; glioma	(74,75)
miR-495	Mesenchymal stem cells	(76)
NVP-LDE-225	Prostate cancer	(32)
PTC-209	Colorectal cancer	(68)

miR, microRNA.

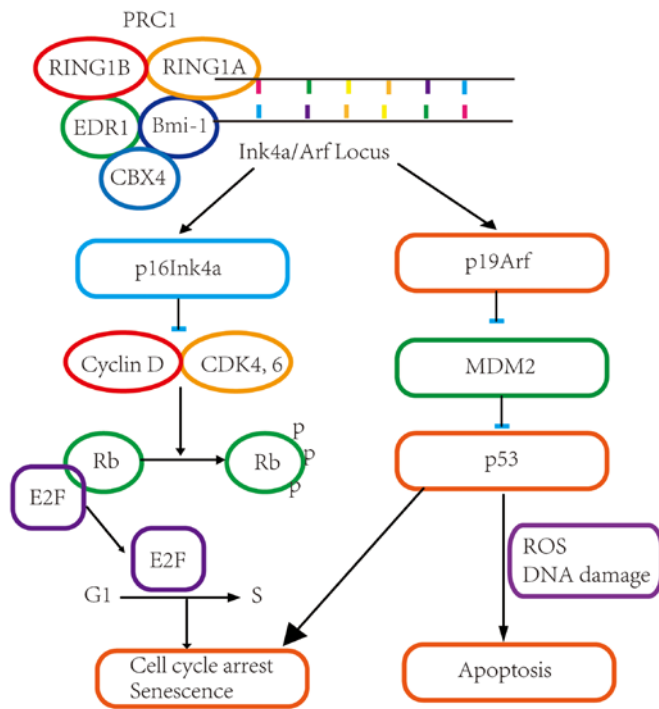


Figure 2. Schematic illustration of the structure of the *BMI-1* gene in homo sapiens, mus musculus and felis catus. NLS, nuclear localization signal; E2F1, E2 promoter binding factor-1; PEST, a peptide sequence that is rich in proline (P), glutamic acid (E), serine (S), and threonine (T).

3. Transcriptional regulation of the *BMI-1* gene

Transcriptional regulation is the primary mechanism by which *BMI-1* expression is controlled. The transcription factors that regulate *BMI-1* include members of the Myc family, Myb, Twist1, SALL4 and E2F-1 (Fig. 3).

Myc family. The Myc family is a group of important oncogenes, including MYC, MYCN, L-Myc, S-Myc and B-Myc. Of these, MYC and MYCN are involved in *BMI-1* transcription (4). MYC plays an important role in cell proliferation, differentiation and apoptosis, and is abnormally expressed in several types of cancer (17). In murine lymphoma and human malignant glioma, both *MYC* and *BMI-1* are highly expressed, and exhibit a positive correlation with each other (18,19). The MYC protein is a transcription factor of the basic helix-loop-helix leucine zipper family. MYC forms a functional DNA-binding complex with Max, another member of the same family, and this complex specifically recognizes the E-box sequence (CACGTG) of the *BMI-1* gene promoter, thereby increasing the expression of *BMI-1* at the transcriptional level (4,19,20).

Another member of the Myc family, *MYCN*, is frequently upregulated in human neuroblastoma (21). *MYCN* protein has been shown to be associated with Bmi-1 expression in orthotopic neuroblastoma cell lines and tumor samples. In addition, *MYCN* protein expression was shown to increase the transcriptional activity of *BMI-1* gene by binding to the *BMI-1* promoter E-box region (22). Overexpression of *MYCN* promotes tumorigenesis and proliferation of neuroblastoma cells by directly targeting and upregulating *BMI-1* (23).

Other factors regulate *BMI-1* indirectly through the Myc gene family. Mel-18 protein is a member of the PcG family

that possesses close structural similarities with the Bmi-1 protein (24); however, functionally, it cannot replace the role of Bmi-1 in PRC1 (6). Mel-18 inhibits transcriptional expression of c-Myc and prevents c-Myc from binding to the *BMI-1* gene promoter (4,25), which indirectly inhibits *BMI-1* transcription. Mel-18 is considered a tumor suppressor due to its ability to inhibit the transcription of the *MYC* and *BMI-1* genes, thereby inhibiting the proliferation and inducing apoptosis of cancer cells (20). Induction of overexpression of Mel-18 to downregulate the expression of *BMI-1* gene was shown to attenuate the malignant attributes of breast cancer cells (26). Furthermore, transcription factor FoxM1c was shown to indirectly increase the expression of *BMI-1* via c-Myc (27,28).

MYB. c-Myb is a member of the *MYB* transcription factor family. It promotes the expression of gut stem cell genes, particularly *Lgr5*, which affects the self-renewal capacity of intestinal and hematopoietic stem cells (29). In B-lymphocytic leukemia cells, c-Myb binds to the E-box element in the proximal regulatory region of the miR-155 host gene promoter, facilitating its transcription (30). Waldron *et al* (31) found that c-Myb binds directly to the +3 to +8 nucleotide sequence of the *BMI-1* 5' flanking region to increase *BMI-1* transcription, and that c-Myb and *Bmi-1* are required for human and mouse p190 BCR/ABL leukemogenesis.

Twist1. Twist1 belongs to the family of basic helix-loop-helix transcription factors. It promotes EMT by inhibiting E-cadherin expression (32). Mechanistically, Twist1 binds directly to the E-cadherin promoter to inhibit its expression, and it also directly binds to the E-box site of the -732 to -727 nucleotide sequence in intron 1 of the *BMI-1* promoter to initiate the transcriptional upregulation of the *BMI-1* gene (5). Twist1-mediated suppression of E-cadherin and upregulation of Bmi-1 leads to disruption of the tight junction between cells, thereby increasing tumor cell metastasis (33,35).

Sal-like protein 4 (SALL4). SALL4 is a more recently identified zinc finger transcription factor that plays an important role in the maintenance of pluripotency of embryonic stem cells and the self-renewal capacity of hematopoietic stem cells (36). Significant upregulation of SALL4 and Bmi-1 expression has been reported in patients with myeloid leukemia (37). Additionally, high expression levels of these two genes were shown to be associated with the expansion of hematopoietic progenitor cells. This suggests that the expression of SALL4 and Bmi-1 is a prognostic biomarker of acute leukemia. Results of luciferase reporter assays by Yang *et al* (36) showed that the *BMI-1* gene is a target of SALL4, and, increased expression of SALL4 was found to upregulate the activity of the *BMI-1* promoter. Further analysis of the binding sites revealed that the SALL4 protein binds to a functional site in the -450 to -1 nucleotide sequence of the *BMI-1* promoter to initiate transcription of the *BMI-1* gene.

E2 promoter binding factor (E2F)-1. E2F-1 is a member of the E2F transcription factor family. E2F-1 is involved in cell cycle progression and regulates cell viability via both p53-independent and p53-dependent pathways (38). E2F-1 initiates transcription of the *BMI-1* gene and upregulates

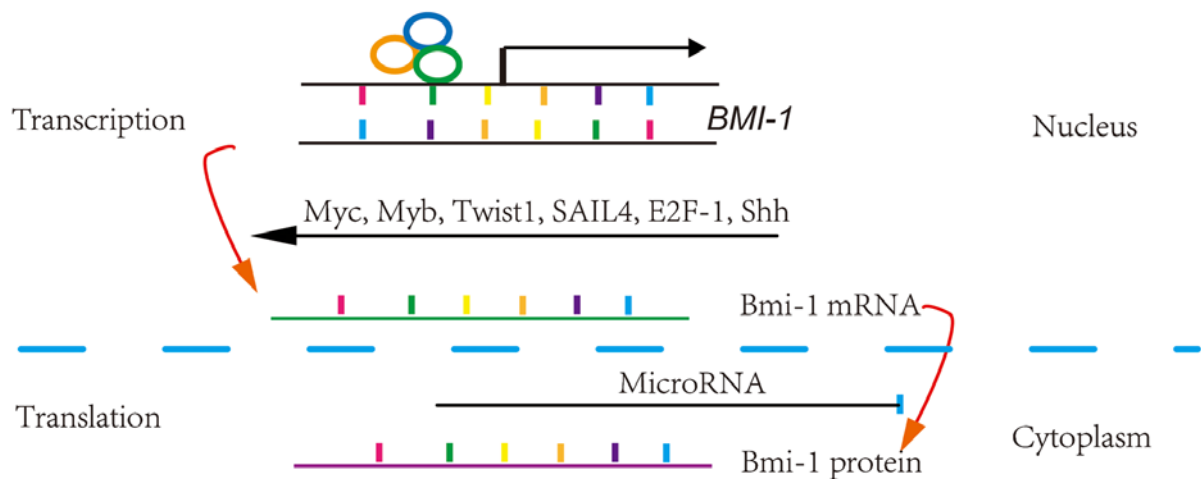


Figure 3. Regulation of BMI-1 expression. The transcription of *BMI-1* is regulated by Myc, Myb, Twist1, SALL4, E2F1, Shh. The translation of *BMI-1* is regulated by various microRNAs. E2F, E2 promoter binding factor; Shh, sonic hedgehog; SALL4, Sal-like protein 4.

BMI-1 expression by directly binding to the E2F binding site in the *BMI-1* gene promoter; interestingly, when the cell is in the cell cycle or differentiation phase, *BMI-1* is not regulated by E2F-1 (39). In androgen-deficient prostate cancer cells, the I κ B kinase α (IKK α)-E2F1-Bmi-1 cascade is activated. In these cells, activated IKK α phosphorylates E2F-1 to promote E2F-1 nuclear localization, whereby E2F-1 binds to the co-activator CREB binding protein (histone H3 acetyltransferase) and recruits the target genes, including *BMI-1*, thereby resulting in activation of *BMI-1* (40).

Hedgehog signaling. Hedgehog signaling is a major regulator of vertebrate embryonic development, as it is involved in stem cell maintenance and cell differentiation and proliferation. Abnormal activation of the Hedgehog signaling pathway was shown to be associated with the development of lung, prostate and breast cancer (41). The primary components of the Hedgehog signaling pathway include patched, Smoothened and glioma-associated oncogene (GLI) (42). In a study by Liu *et al* (43), addition of sonic Hedgehog to activate the Hedgehog signaling pathway increased the expression of Bmi-1, whereas inhibition of the Hedgehog signaling pathway using cyclopamine resulted in downregulated expression of Bmi-1. Wang *et al* (44) found that GLI1 binds to the promoter of the *BMI-1* gene, and that the *BMI-1* transcription level changes in accordance with the increase or decrease in GLI1 expression.

Other factors. In addition to the above transcription factors, several other factors may regulate *BMI-1*. Estrogen receptor α activates the transcriptional activity of the *BMI-1* gene by interacting with the -327 to -172 bp nucleotide sequence upstream of the *BMI-1* promoter, thereby increasing *BMI-1* gene expression (45). The transcription factor Sp1 binds to the +181 to +214 region of the *BMI-1* promoter and increases *BMI-1* gene expression (46). Krüppel-like factor 4 (KLF4) is a zinc finger protein that is normally expressed in the intestines and skin, and plays an important role in the regulation of stem cells. Yu *et al* (47) found that KLF4 binds directly to the -233 to 0 sequence of the *BMI-1* gene promoter and inhibits the

transcriptional activity of *BMI-1*, thereby reducing the expression of Bmi-1. The binding site of KLF4 to the *BMI-1* gene is different from the binding site of c-Myc to the *BMI-1* promoter. Redox sensing factor Nrf2 was shown to increase the expression of *BMI-1* at the transcriptional level, thereby promoting the proliferation of cancer stem cells and inhibiting cancer cell apoptosis (48). The helix-loop-helix inhibitor of differentiation and DNA binding facilitates tumorigenesis by increasing the expression of Bmi-1 via c-Myc (49). Bommi *et al* (50) found that histone deacetylase inhibitors (HDACi) inhibit *BMI-1* gene transcription in breast cancer cells via an indirect mechanism. In certain cancer cell lines, c-Myc is the target gene of HDACi, whereas in breast cancer cells, the inhibitory effect of HDACi on *BMI-1* gene expression is not dependent on down-regulation of c-Myc; however, the precise mechanism is not clear. Thus, there are various transcription factors that bind the promoter of *BMI-1* and regulate *BMI-1* gene expression at the transcriptional level.

4. Regulation of Bmi-1 at the post-transcriptional level

Post-transcriptional regulation primary involves the regulation of RNA and is divided into the following steps in chronological order: RNA processing and maturation, RNA transport and subcellular localization, mRNA translation and mRNA degradation. MicroRNAs (miRNAs) block gene expression primarily by preventing mRNA translation and/or promoting mRNA degradation (51). miRNAs are non-coding, short-stranded RNAs, which typically consist of 18-22 nucleotides. An miRNA complements the 3'-untranslated region (UTR) of its target mRNA and directs RNA-induced silencing complex to a specific region of the mRNA, thereby inhibiting mRNA translation or promoting mRNA degradation (8).

Bmi-1 expression is inhibited by several miRNAs, including miR-135a, miR-141, miR-183, miR-15a, miR-194, miR-203, miR-200b, miR-320a, miR-200c, miR-16, miR-495, miR-221, miR-30d, miR-128a, miR-34a, miR-452, miR-302 and miR-30e (51-67). For example, the expression of miR-218 in cancer tissues is lower than that in the paratumoral normal

tissues, whereas the expression of Bmi-1 in cancer tissues is higher than that in the paratumoral normal tissues. An inverse correlation between Bmi-1 expression and miR-128 has been demonstrated in glioma and rectal cancer cells. Results of luciferase reporter assays showed that miR-128 inhibits Bmi-1 protein expression by binding to the 476 to 488 region of *BMI-1* 3'-UTR (54). Several transcription factors and cytokines affect the expression levels of Bmi-1 by altering the expression of miRNAs. For example, Zeb1 was shown to downregulate Bmi-1 expression by inducing upregulation of the expressions of miR-203 and miR-183 (32).

5. Conclusion and future prospects

The polycomb family protein member Bmi-1 acts as an oncogene and maintains the undifferentiated state of malignant tumor cells. Bmi-1 expression levels are closely related to the degree of malignancy, invasion and metastasis, and is a biomarker of adverse prognosis in cancer patients. As a pivotal node of multiple signaling pathways, Bmi-1 regulates the function of several downstream transcription factors and cytokines. Therefore, inhibition of Bmi-1 expression is a promising strategy for anticancer drug development. It has been shown that NVP-LDE-225 (Erismodegib) inhibits Bmi-1 expression by inducing upregulation of miR-128 (68). In addition, PTC-209 is a small molecule drug that specifically inhibits Bmi-1 expression at the post-transcriptional level by binding to the 5' and 3' non-coding regions of *BMI-1* mRNA (69). Transcriptional and post-transcriptional regulation are the primary means of regulation of Bmi-1 expression. Therefore, regulatory factors are potential therapeutic targets to reduce Bmi-1 expression in cancer cells.

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Availability of data and materials

Not applicable.

Authors' contributions

MZ and QX searched the literature, reviewed the articles and collected the relevant data from the selected papers. DH and LL wrote the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

All authors declare no competing interests.

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