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

MEIZHEN ZHOU, QICHAO XU, DEQIANG HUANG and LINGYU LUO

Department of Gastroenterology, Research Institute of Digestive Diseases, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, P.R. China

Received June 19, 2020; Accepted February 19, 2021

DOI: 10.3892/br.2021.1428

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 transcription 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.

Contents
1. Introduction
2. Bmi-1 protein structure
3. Transcriptional regulation of the BMI-1 gene
4. Regulation of Bmi-1 at the post-transcriptional level
5. Conclusion and future prospects

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 complex 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); IKKα, IκB 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

Regulation of gene transcription of B lymphoma Mo-MLV insertion region 1 homolog (Review)
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 (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 *BMI-1* promoter | (18,19) |
| N-Myc            | Increases Bmi-1 expression by binding to the E-box sequence in the *BMI-1* 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 *BMI-1* gene | (3)     |
| SALL4            | Binds to the -450 to -1 region of the *BMI-1* promoter and increases *Bmi-1* transcription | (36)    |
| E2F-1            | Combines with the E2F-1 binding site in *BMI-1* promoter to increase *Bmi-1* transcriptional activity | (38,40) |
| Hedgehog signal  | Hedgehog downstream protein GLI1 binds to BMI-1 promoter and increases Bmi-1 transcription | (44)    |
| FoxM1c           | Promotes Bmi-1 expression by increasing c-Myc expression                  | (28)    |
| Estrogen receptor α | Interacts with the *BMI-1* promoter upstream element at -327 to -172 bp to activate *BMI-1* transcription | (45)    |
| Sp1              | Binds to the region from +181 to +214 within the *BMI-1* promoter and increases *BMI-1* transcriptional activity | (46)    |
| Nrf2             | Promotes *BMI-1* 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 *BMI-1* promoter activity                             | (50)    |
| KLF4             | Binds to the *BMI-1* promoter sequence, -233 to 0, to suppress *BMI-1* 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)    |
| miR-16  | Prostate tumor tissues                                                               | (71)    |
| miR-30d | Ovarian cancer tissues                                                               | (53,66) |
| miR-30e | 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.
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 gene by binding to the promoter E-box region (22). Overexpression of BMI-1 promoter E-box region (22). Overexpression of MYCN protein was shown to increase transcription of the BMI-1 gene, thereby increasing cell cycle progression and regulating cell viability via both p53-dependent and p53-independent pathways (27). Consequently, MYC and BMI-1 play a crucial role in the maintenance of pluripotency of embryonic stem cells (36).

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-Myc 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-Myc 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-Myc binds directly to the +3 to +8 nucleotide sequence of the BMI-1 promoter to initiate BMI-1 transcription, and that c-Myc 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...
**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 IκB kinase α (IKKα)-E2F1-Bmi-1 cascade is activated. In these cells, activated IKKα 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 Spi1 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 (Erismodiegib) 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.

Acknowledgements

Not applicable.

Funding

This study was supported by the National Nature Science Foundation of China (grant no. 82060450), Nature Science Foundation of Jiangxi province of China (grant nos. 20192BAB205072 and 20181BAB205050), and The Education Department of Jiangxi Province of China (grant no. 160032).

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.

References

1. Park IK, Qian D, Kiel M, Becker MW, Pialhja M, Weissman IL, Morrison SJ and Clarke MF: Bmi-1 is required for maintenance of self-renewing haematopoietic stem cells. Nature 423: 302-305, 2003.
2. Park IK, Morrison SJ and Clarke MF: Bmi1, stem cells, and senescence regulation. J Clin Invest 113: 175-179, 2004.
3. Yang MH, Hsu DS, Wang HW, Wang HJ, Lan HY, Yang WH, Huang CH, Kao SY, Tseng CH, Tai SK, et al: Bmi1 is essential in Twist1-induced epithelial-mesenchymal transition. Nat Cell Biol 12: 982-992, 2010. Erratum in: Nat Cell Biol 21: 533, 2019.
4. Adhikary S and Eilers M: Transcriptional regulation and transformation by Myc proteins. Nat Rev Mol Cell Biol 6: 635-645, 2005.
5. Kim J, Hwangbo J and Wong PK: p38 MAPK-Mediated Bmi-1 down-regulation and defective proliferation in ATM-deficient neural stem cells can be restored by Akt activation. PLoS One 6: e16615, 2011.
6. Cao R, Tsukada Y and Zhang Y: Role of Bmi-1 and Ring1A in H2A ubiquitylation and Hox gene silencing. Mol Cell 20: 845-854, 2005.
7. Bhattacharyya J, Mihara K, Ohtsubo M, Yasunaga S, Takei Y, Yanagihara K, Sukai A, Hoshi M, Takihara Y and Kimura A: Overexpression of BMI-1 correlates with drug resistance in B-cell lymphoma cells through the stabilization of survivin expression. Cancer Sci 103: 34-41, 2012.
8. Cao L, Bombard J, Cintron K, Sheedy J, Weetall ML and Davis TW: Bmi1 as a novel target for drug discovery in cancer. J Cell Biochem 112: 2729-2741, 2011.
9. Venkatesh S and Workman JL: Histone exchange, chromatin structure and the regulation of transcription. Nat Rev Mol Cell Biol 16: 178-189, 2015.
10. Siddique HR, Parraw A, Tarapore RS, Wang L, Mukhtar H, Karnes RJ, Deng Y, Konety BR and Saleem M: BMI1 polycomb group protein acts as a master switch for growth and death of tumor cells: Regulates TCF4-transcriptional factor-induced BCL2 signaling. PLoS One 8: e60664, 2013.
11. Alkema MJ, Wiegant J, Raap AK, Berns A and van Lohuizen M: Characterization and chromosomal localization of the human proto-oncogene BMI-1. Hum Mol Genet 2: 1597-1603, 1993.
12. Freemont PS, Hanson IM and Trowsdale J: A novel cysteine-rich sequence motif. Cell 64: 483-484, 1991.
13. Dimri GP, Martinez JL, Jacobs JL, Keblusek P, Itahana K, Van Lohuizen M, Campisi J, Wazer DE and Band V: The BMI-1 oncogene induces telomererase activity and immortalizes human mammary epithelial cells. Cancer Res 62: 4736-4745, 2002.
14. Cohen KJ, Hanna JS, Prescott JE and Dang CV: Transformation by the Bmi-1 oncogene correlates with its subnuclear localization but not its transcriptional suppression activity. Mol Cell Biol 16: 5527-5535, 1996.
15. Buchwald G, van der Stoop P, Weichenrieder O, Perrakis A, van Lohuizen M and Sixma TK: Structure and E3-ligase activity of the Ring-Ring complex of polycomb proteins Bmi1 and Ring1b. EMBO J 25: 2465-2474, 2006.
16. Rogers S, Wells R and Rechsteiner M: Amino acid sequences common to rapidly degraded proteins: The PEST hypothesis. Science 234: 364-368, 1986.
17. Hoffmann B and Liebermann DA: Apoptotic signaling by c-MYC. Oncogene 27: 6462-6472, 2008.
18. Jacobs JL, Scheijen B, Vonchenk JW, Kieboom K, Berns A and van Lohuizen M: Bmi-1 collaborates with c-Myc in tumorigenesis by inhibiting c-Myc-induced apoptosis via INK4a/ARF. Genes Dev 13: 2678-2690, 1999.
19. Cenci T, Martin M, Montano N, D'Alessandris GG, Falchetti ML, Annibali D, Savino M, Bianchi F, Pierconti F, Nasi S, et al: Prognostic relevance of c-Myc and BMI1 expression in patients with glioblastoma. Am J Clin Pathol 138: 390-396, 2012.
20. Guo WJ, Datta S, Band V and Dimri GP: Mel-18, a polyclonal group protein, regulates cell proliferation and senescence via transcriptional repression of Bmi-1 and c-Myc oncogenes. Mol Cell Biol 18: 536-546, 2007.

21. Weiss WA, Aldape K, Mohapatra G, Feuerstein BG and Bishop JM: Targeted expression of MYCN causes medulloblastoma in transgenic mice. EMBO J 16: 2985-2997, 1997.

22. Ochiai H, Takenobu H, Nakagawa A, Yamaguchi Y, Kimura M, Oh M, Okumura Y, Okino Y, Kihara A and Yamasaki S: Bmi-1 is a MYCN target gene that regulates tumorigenesis through repression of Klf1 and Tsc1 in neuroblastomas. Oncogene 29: 2601-2609, 2010.

23. Huang R, Cheung NKV, Vider J, Cheung JY, Gerald WL, Tsang W, Liang EC and Blagbrough RG: MYCN and MYC regulate tumor proliferation and tumorigenesis directly through Bmi1 in human neuroblastomas. FASEB J 25: 4138-4149, 2011.

24. Ishida A, Asano H, Hasegawa M, Koseki H, Ono T, Yoshida MC, Tanigawa K, Manno M: Cloning and chromosome mapping of the human Mel-18 gene which encodes a DNA-binding protein with a new ‘RING-finger’ motif. Gene 129: 249-255, 1993.

25. Tetsu O, Ishihara H, Kanno R, Kiyasu M, Inoue H, Tokuhisa T, Taniguchi M and Kanno M: mel-18 negatively regulates cell cycle progression upon B cell antigen receptor stimulation through a cascade leading to c-myc/cdc25. Immunity 9: 439-448, 1999.

26. Guo WJ, Zeng MS, Yadav A, Song LB, Guo BH, Band V and Dimri GP: Mel-18 acts as a tumor suppressor by repressing Bmi-1 expression and down-regulating Akt activity in breast cancer cells. Oncol Rep 57: 5033-5041, 2007.

27. Liu-Bryan R and Terkeltaub R: Chondrocyte innate immune myeloid differentiation factor 88-dependent signaling drives procathepsin D expression of the endogenous Toll-like receptor 2/Toll-like receptor 4 ligands low molecular weight hyaluronan and high mobility group box chromosomal protein 1 in mice. Arthritis Rheum 62: 2004-2012, 2010.

28. Li SKM, Smith DK, Leung WY, Cheung AM, Lam EW, Dimri GP: The polycomb group protein BMI1 is a transcriptional target of HDAC inhibitors. Cell Cycle 9: 2663-2673, 2010.

29. Tetsu O, Ishihara H, Kanno R, Kiyasu M, Inoue H, Tokuhisa T, Taniguchi M and Kanno M: Cloning and chromosome mapping of the human Mel-18 gene which encodes a DNA-binding protein with a new ‘RING-finger’ motif. Gene 129: 249-255, 1993.

30. Yui T, Chen X, Zhang W, Colon D, Shi J, Napier D, Rybachou P, Lu W, Lee EY, Weiss HL, et al: Regulation of the potential marker for intestinal cells, Bmi1, by β-catenin and the zinc finger protein KLF4; Implications for colon cancer. J Biol Chem 287: 16768-16776, 2012.

31. Yui T, Chen X, Zhang W, Colon D, Shi J, Napier D, Rybachou P, Lu W, Lee EY, Weiss HL, et al: Regulation of the potential marker for intestinal cells, Bmi1, by β-catenin and the zinc finger protein KLF4; Implications for colon cancer. J Biol Chem 287: 16768-16776, 2012.

32. wang HB, Liu GH, Zhang H, Xing S, Hu LJ, Zhao WF, Xie B, Li MZ, Zeng BH, Li Y, et al: Sp1 and c-Myc regulate transcription of Bmi1 in nasopharyngeal carcinoma. FEBS J 270: 2929-2944, 2013.

33. Gupta S, Takebe N and Lorosso P: Targeting the Hedgehog pathway in cancer, Ther Adv Med Oncol 2: 237-250, 2010.

34. Briscoe J and Thérond PF: The mechanisms of Hedgehog signalling and its role in development and disease. Nat Rev Mol Cell Biol 14: 416-429, 2013.

35. Liu S, Douta G, Mantle ID, Patel S, Ahn NS, Jackson KW, Suri P and Wicha MS: Hedgehog signaling and Bmi-1 regulate self-renewal of normal and malignant human mammary stem cells. Cancer Res 66: 4827-4831, 2006.

36. Wang X, Venugopal C, Manoranjan B, McFarlane N, O'Farrell E, Nolte S, Gunnarsson T, Hollenberg R, Kwiecien J, Northcott P, et al: Sonic hedgehog regulates Bmi1 in human medulloblastoma brain tumor-initiating cells. Oncogene 31: 187-199, 2012.

37. Wang H, Liu H, Li X, Zhao J, Zhang H, Mao J, Zou Y, Zhang H, Zhang S, Hou W, et al: Estrogen receptor α-coupled Bmi1 regulation pathway in breast cancer and its clinical implications. BMC Cancer 14: 122, 2014.

38. Wang HB, Liu GH, Zhang H, Xing S, Hu LJ, Zhao WF, Xie B, Li MZ, Zeng BH, Li Y, et al: Sp1 and c-Myc regulate transcription of Bmi1 in nasopharyngeal carcinoma. FEBS J 270: 2929-2944, 2013.

39. Yu T, Chen X, Zhang W, Colon D, Shi J, Napier D, Rybachou P, Lu W, Lee EY, Weiss HL, et al: Regulation of the potential marker for intestinal cells, Bmi1, by β-catenin and the zinc finger protein KLF4; Implications for colon cancer. J Biol Chem 287: 16768-16776, 2012.

40. Jia Y, Chen J, Zhu H, Jia ZH and Cui MH: Abruptly elevated redox sensing factor Nrf2 promotes cancer stem cell survival via enhanced transcriptional regulation of ABCG2 and Bcl-2/Bmi-1. Oncol Rep 34: 2290-2304, 2015.

41. Qin T, Lee JY, Park JH, Kim JH and Kong G: Id1 enhances RING1 ubiquitin ligase activity through the Mel-18/Bmi1 polycomb group complex. Oncol Rep 29: 5818-5827, 2010.

42. Bommi PV, Dimri M, Sahasrabuddhe AD, Khandekar J and Dimri GP: The polycomb group protein BMI1 is a transcriptional target of HDAC inhibitors. Cell Cycle 9: 2663-2673, 2010.

43. Slaby O, Svoboda M, Michalek J and Vyzula R: MicroRNAs in colorectal cancer: Translation of molecular biology into clinical application. Mol Cancer 9: 59, 2010.

44. Bhattacharyya J, Mihara K, Yasunaga S, Tanaka H, Hoshi M, Takihara Y and Kimura A: BMI-1 expression is enhanced through transcriptional and posttranscriptional regulation during the progression of chronic myeloid leukemia. Ann Hematol 88: 333-340, 2009.

45. Ambros V: The functions of animal microRNAs. Nature 431: 350-355, 2004.

46. Godlewski J, Nowicki MO, Bronisz A, Williams S, Otsuki A, Nuovo G, Raychaudhury A, Newton HB, Chiocca EA and Laval J: Targeted expression of a microRNA-128 factor by microRNA-128 inhibits glioma proliferation and self-renewal. Mol Cancer 8: 350-355, 2009.

47. He X, Dong Y, Wu CW, Zhao Z, Ng SS, Chan FK, Sung JJ and Yu H: MicroRNA-218 inhibits cell cycle progression and promotes apoptosis in colon cancer by downregulating BMI1 polycomb ring finger oncogene. Mol Med 18: 1491-1498, 2013.

48. Dang Z, Xu WH, Lu P, Wu N, Liu J, Ruan B, Zhou L, Song WJ and Dou KF: MicroRNA-135a inhibits cell proliferation by targeting BMI1 in pancreatic ductal adenocarcinoma. Int J Biol Sci 10: 733-745, 2014.

49. Xu L, Li Y, Yan D, He J and Liu D: MicroRNA-183 inhibits gastric cancer proliferation and invasion via directly targeting BMI-1. Oncol Lett 8: 2345-2351, 2014.

50. Wu C, Zheng X, Li X, Fesler A, Hu W, Chen L, Xu B, Wang Q, Tong A, Burke S, et al: Reduction of gastric cancer proliferation and invasion by miR-15a mediated suppression of BMI-1 transcription. Oncotarget 7: 14522-14536, 2016.

51. Dong P, Kaneki M, Watari H, Hamada J, Sudo S, Ju J and Sakuragi N: MicroRNA-194 inhibits epithelial to mesenchymal transition of endometrial cancer cells by targeting oncogene BMI-1. Mol Cancer 10: 99, 2011.

52. Dimri G, Carroll JD, Cho JH and Dimri GP: microRNA-141 regulates BMI1 expression and induces senescence in human diploid fibroblasts. Cell Cycle 12: 3537-3546, 2013.

53. Sugihara H, Ishimoto T, Watanabe M, Sawayama H, Iwatsuki M, Baba Y, Komohara Y, Takeya M and Baba H: Identification of miRNA is angiogenic and neovascular inducing functions in vitro. Cardiovasc Res 74: 410-415, 2007.

54. Liu S, Douta G, Mantle ID, Patel S, Ahn NS, Jackson KW, Suri P and Wicha MS: Hedgehog signaling and Bmi-1 regulate self-renewal of normal and malignant human mammary stem cells. Cancer Res 66: 4827-4831, 2006.

55. Wang X, Venugopal C, Manoranjan B, McFarlane N, O'Farrell E, Nolte S, Gunnarsson T, Hollenberg R, Kwiecien J, Northcott P, et al: Sonic hedgehog regulates Bmi1 in human medulloblastoma brain tumor-initiating cells. Oncogene 31: 187-199, 2012.
Zhang Y, Zhou SY, Yan HZ, Xu DD, Chen HX, Wang XY, Wang X, Liu YT, Zhang L, Wang S, et al: miR-203 inhibits proliferation and self-renewal of leukemia stem cells by targeting survivin and Bmi-1. Sci Rep 6: 19995, 2016.

Qi X, Li J, Zhou C, Lv C and Tian M: MicroRNA-320a inhibits cell proliferation, migration and invasion by targeting BMI-1 in nasopharyngeal carcinoma. FEBS Lett 588: 3732-3738, 2014.

Liu S, Tetzlaff MT, Cui R and Xu X: miR-200c inhibits melanoma progression and drug resistance through down-regulation of BMI-1. Am J Pathol 181: 1823-1835, 2012.

Bhattacharya R, Nicoloso M, Arvizo R, Wang E, Cortez A, Rossi S, Calin GA and Mukherjee P: miR-15a and miR-16 control Bmi-1 expression in ovarian cancer. Cancer Res 69: 9090-9095, 2009.

Venkataraman S, Alimova I, Fan R, Harris P, Foreman N and Vihakar R: MicroRNA 128a increases intracellular ROS level by targeting Bmi-1 and inhibits medulloblastoma cancer cell growth by promoting senescence. PLoS One 5: e10748, 2010.

Nanta R, Kumar D, Meeker D, Rodova M, Van Velthuizen PJ, Shankar S and Srivastava RK: NVP-LDE-225 (Erismodegib) inhibits epithelial-mesenchymal transition and human prostate cancer stem cell growth in NOD/SCID IL2RG null mice by regulating Bmi-1 and microRNA-128. Oncogenesis 2: e42, 2013.

Kreso A, van Galen P, Pedley NM, Lima-Fernandes E, Frelin C, Davis T, Cao L, Baiazitov R, Du W, Sydorenko N, et al: Self-renewal as a therapeutic target in human colorectal cancer. Nat Med 20: 29-36, 2014.

Li Y, Hu J, Guan F, Song L, Fan R, Zhu H, Hu X, Shen E and Yang B: Copper induces cellular senescence in human glioblastoma multiforme cells through downregulation of Bmi-1. Oncol Rep 29: 1805-1810, 2013.