BMI-1, a promising therapeutic target for human cancer (Review)

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Abstract. *BMI-1* oncogene is a member of the polycomb-group gene family and a transcriptional repressor. Overexpression of BMI-1 has been identified in various human cancer tissues and is known to be involved in cancer cell proliferation, cell invasion, distant metastasis, chemosensitivity and patient survival. Accumulating evidence has revealed that BMI-1 is also involved in the regulation of self-renewal, differentiation and tumor initiation of cancer stem cells (CSCs). However, the molecular mechanisms underlying these biological processes remain unclear. The present review summarized the function of BMI-1 in different human cancer types and CSCs, and discussed the signaling pathways in which BMI-1 is potentially involved. In conclusion, BMI-1 may represent a promising target for the prevention and therapy of various cancer types.

Contents

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Abbreviations: CSCs, cancer stem cells; PcG, polycomb group

Key words: therapeutic target, BMI-1, human cancer, cancer stem cells, poor prognosis

1. Introduction

At present, the success of cancer treatment is challenging and one of the key determinants of treatment failure may be the presence of cancer stem cells (CSCs) (1). This small proportion of tumor cells plays a pivotal role in tumor growth, proliferation, invasion, distant metastasis and relapse of numerous types of cancer (2). Therefore, identifying a reliable biomarker that is associated with the treatment of human cancer and CSCs is important.

The role of oncogenic *BMI-1* (also known as B-lymphoma Moloney murine leukemia virus insertion region-1), a member of the polycomb-group (PcG) family of proteins, in cancer has attracted increasing attention. Biehs *et al* have demonstrated that BMI-1 was important in the maintenance of stem cell properties in a mouse incisor model (3). Certain studies have also revealed that BMI-1 was involved in the self-renewal, differentiation and tumor initiation of CSCs (3-5). In addition, BMI-1 is known to be upregulated in various human cancer tissues and is important in the regulation of malignant transformation, proliferation, cell cycle, apoptosis and distant metastasis (6). The present review summarized the role of BMI-1 in human cancer and CSCs, and discussed the signaling pathways in which BMI-1 is involved. Furthermore, the potential of BMI-1 as a critical prognostic marker, as well as a future therapeutic target, was reviewed.

2. BMI-1 and cancer

BMI-1 was first identified in a B-cell lymphoma as a transcriptional repressor that was a member of the PcG transcription factors (7). Overexpression of BMI-1 has been previously reported in gastric, ovarian, breast, head and neck, pancreatic and lung cancer, as well as in primary hepatocellular carcinoma (HCC) and endometrial carcinoma (8-16). In addition, BMI-1 overexpression has been identified in patients suffering from myelodysplastic syndrome, chronic myeloid leukemia, acute myeloid leukemia and lymphoma (17-20). Previous studies have indicated that the increased BMI-1 expression was associated with tumor proliferation, invasion/metastasis, chemosensitivity and patient survival (Table I).

Numerous studies have indicated that BMI-1 may promote tumor cell growth (Table I). The overexpression of BMI-1 in gastric and breast cancer has been identified to promote cell growth and proliferation, inhibit apoptosis and

Table I. Effects of BMI-1 expression in different tumor types.

	In vitro				*In vivo* (patients)			
Tumor type	Cell proliferation	Cell invasion	Chemosensitivity	Refs	Tumor metastasis	Patient survival	Drug resistance	Refs
Gastric cancer	(+)	(+)	ND	(6,7)	(+)	ND	(+)	(16,17)
Hepatocellular carcinoma	ND	(+)	(+)	(13,30)	(+)	ND	ND	(13)
Pancreatic cancer	(+)	(+)	(+)	(8-11)	(+)	(+)	ND	(8)
Lung cancer	(+)	ND	ND	(12)	(+)	(+)	ND	(18-20)
Endometrial carcinomas	ND	(+)	ND	(15)	(+)	ND	ND	(22)
Ovarian cancer	ND	ND	(+)	(31,32)	(+)	(+)	ND	(4,40)
Breast cancer	(+)	ND	ND	(4)	(+)	ND	(+)	(26-29,38,39)
Head and neck cancer	ND	(+)	ND	(14)	(+)	(+)	ND	(23-25)
Hematological malignancy	ND	ND	(+)	(37)	(+)	(+)	(+)	(33-36)

Refs, references; ND, no data available; (+), positive correlation.

enhanced clone formation capability (6,21,22). By contrast, the depletion of BMI-1 in certain pancreatic cancer cell lines was found to suppress cell proliferation, sensitize apoptosis and inhibit tumor formation in nude mice (13,23-25). In addition, upregulation of BMI-1 expression enhanced the ability of colony formation in a soft agar assay in non-small cell lung cancer (NSCLC) tissues (26).

Invasion/metastasis of cancer is commonly associated with poor prognosis in patients. Strong evidence supports the involvement of BMI-1 in tumor cell invasion in gastric cancer, primary HCC, pancreatic cancer, endometrial carcinoma, and head and neck cancer (Table I). Overexpression of BMI-1 in gastric cancer resulted in increased migration and invasion abilities (21,22), while BMI-1 depletion reduced the invasiveness of HCC cells (15). Song *et al* also identified that upregulation of BMI-1 expression enhanced the motility and invasiveness of human nasopharyngeal epithelial cells, whereas silencing of BMI-1 expression reduced motility (27). Epithelial-mesenchymal transition (EMT) is the key process driving cancer metastasis and BMI-1 has been demonstrated to induce EMT in endometrial carcinoma cells (28). Furthermore, *in vivo* studies revealed that BMI-1 expression was upregulated in cancer tissues compared with matched healthy tissues and was associated with distant metastases of gastric cancer (8,29), HCC (15), lung cancer (14,30,31), endometrial carcinomas (16,28,32), and head and neck cancer (11,12,33). Several previous studies have also suggested that BMI-1 contributed to mammary carcinogenesis, axillary lymph node metastases, highly aggressive behavior and late-stage relapse in breast cancer (6,10,34-36).

Drug resistance is an important cause of cancer treatment failure and previous studies have demonstrated that the overexpression of BMI-1 was associated with cancer chemosensitivity (Table I) (9,30,31). Certain *in vitro* studies revealed that overexpression of BMI-1 can promote chemoresistance (23), whereas depletion of BMI-1 is able to enhance the chemosensitivity of HCC (15,37) and ovarian cancer cells (38,39). In a clinical setting, the overexpression of BMI-1 may facilitate drug resistance in hematological malignancies, including the myelodysplastic syndrome, chronic myeloid leukemia, acute myeloid leukemia and lymphoma (17-20,40). In addition, BMI-1 has been demonstrated to play an important role in chemoresistance and radiosensitivity in breast cancer (41,42).

BMI-1 has also been found to be associated with the survival of pancreatic cancer, NSCLC, ovarian carcinoma, head and neck cancer, and hematological malignancy patients (Table I), suggesting that BMI-1 is a significant prognostic factor of poor survival. For instance, Song *et al* investigated the survival of 72 patients with pancreatic cancer and identified that the overexpression of BMI-1 was associated with a significantly reduced overall survival (24). In addition, Yang *et al* studied the BMI-1 expression and survival in a cohort of 179 patients with invasive ovarian carcinoma (9). The authors demonstrated a significant association between increased BMI-1 expression and reduced patient survival (mean, 49 months), when compared with patients presenting a low BMI-1 expression (mean, 100 months; $P<0.001$) (9). Furthermore, Vrzalikova *et al* performed immunohistochemical staining for BMI-1 in 179 NSCLC samples, identifying that the five-year survival rate of BMI-1-positive patients was only 31.2%, in contrast to BMI-1-negative patients that exhibited a survival rate of 50.7% ($P=0.004$) (43).

Overexpression of BMI-1 has also been revealed to correlate with pediatric brain tumors, skin cancer, melanoma, prostate cancer and bladder cancer (44-47). Cancer cell proliferation, invasion/metastasis and chemosensitivity are associated with cancer treatment failure and may induce poor prognosis in patients. However, numerous studies have demonstrated that the treatment failure of various human cancer types is associated with CSCs (3,48). BMI-1 has received increasing attention, since it has been demonstrated to be important in maintaining the properties of CSCs. Therefore, studies further addressing the effect of BMI-1 on CSCs are essential to understand the role of CSCs in human cancer, and may lead to improved treatment strategies.

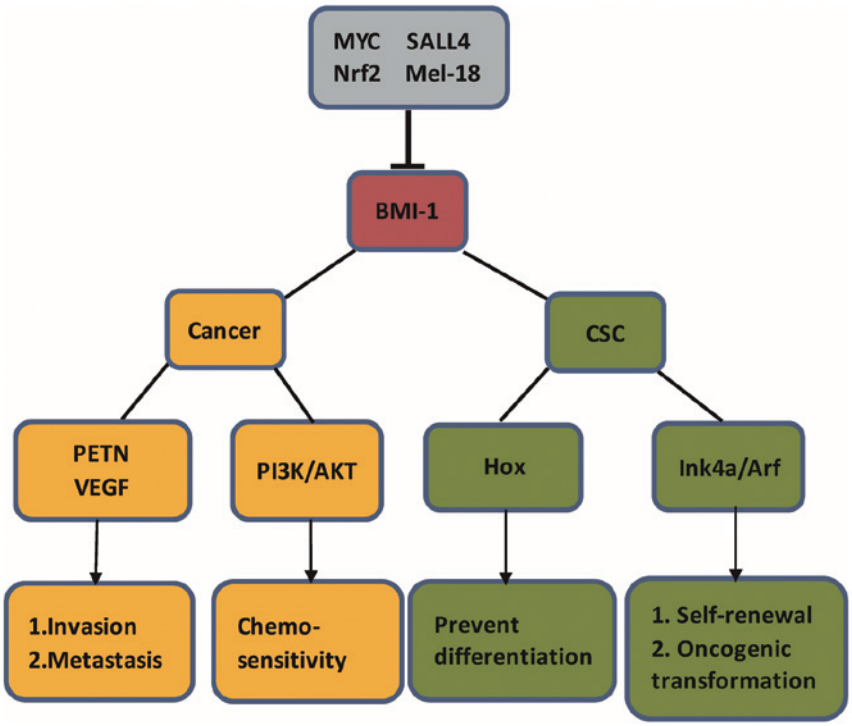

Figure 1. BMI-1 is important in the regulation of cancer and CSCs, functioning through the activation of multiple signaling pathways. BMI-1 expression is upregulated by MYC, SALL4, Nrf2 and is downregulated by Mel-18. BMI-1 regulates cancer cell invasion/metastasis and chemosensitivity by regulating VEGF, PTEN and PI3K/AKT signaling pathway. BMI-1 regulates CSC differentiation through repression of Hox genes, regulates self-renewal and malignant transformation through repression of Ink4a/Arf genes. CSC, cancer stem cell; VEGF, vascular endothelial growth factor. Nrf2, nuclear factor erythroid 2-related factor 2.

3. Association between BMI-1 and CSCs

The CSC hypothesis was first described by Park *et al* (49) in 1971. Advances in CSC isolation were initially achieved in hematological malignancies, with CSCs first detected in acute myeloid leukemia. Subsequently, using similar strategies and technologies, and taking advantage of available surface markers, CSCs have been identified in a range of epithelial and other solid organ malignancies, indicating that these cells are involved in the majority of malignancies (50). CSCs are defined by their extensive self-renewal, differentiation and tumor initiation properties (3-5). Thus, the signaling pathways required for the maintenance of CSCs are candidate targets for a successful molecular therapy of various tumors. Recent studies have demonstrated that BMI-1 is involved in the regulation of CSCs.

BMI-1 is indispensable for the regulation of self-renewal by normal stem cells, leukemic stem cells (LSCs) and hematopoietic stem cells (HSCs) (51-54). For instance, Park *et al* (54) revealed that the number of HSCs in the fetal liver of *BMI-1*-null mice was normal, whereas it was markedly reduced in postnatal *BMI-1*-null mice. In addition, transplanted fetal liver and bone marrow cells obtained from the mice were able to contribute only transiently to hematopoiesis. No self-renewal was detected in adult HSCs, indicating a cell autonomous defect in *BMI-1*-null mice (54) and the importance of BMI-1 in the self-renewal of normal stem cells.

BMI-1 is also indispensable for the regulation of self-renewal in human solid tumors, including oral, esophageal, prostate, pancreatic, neuronal, non-small cell lung and breast cancer (2,26,48,55-58). In order to examine the function of BMI-1 in stem cells, Lukacs *et al* identified that decreased expression of BMI-1 in prostate cells reduced the number and size of spheres formed by these cells, while increased BMI-1 expression enhanced the sphere formation and size (4). Furthermore, Biehs *et al* reported that BMI-1 was expressed by incisor stem cells and that deletion of BMI-1 resulted in a reduced number of stem cells and perturbed gene expression (3). BMI-1 is known to be highly enriched in CD133-positive cells of human glioblastoma multiforme (GBM). A previous cell biology study revealed that BMI-1 prevents CD133-positive cell apoptosis and differentiation into neurons and astrocytes (5). In addition, the study demonstrated that BMI-1 is involved in GBM tumor growth and required to sustain CSC renewal and differentiation (5).

CSCs are associated with tumor initiation and malignant transformation. Previous studies demonstrated that BMI-1 plays an important role in these processes. For instance, in breast cancer, CSCs were no longer able to initiate tumors following the knocking down of BMI-1 expression by short hairpin RNA (59). However, tumor initiation was rescued with the introduction of a BMI-1 overexpression vector in the BMI-1 knockdown cells (59). In a clinical setting, a high expression of BMI-1 is associated with precancerous lesions of esophageal adenocarcinoma (60) and oral cancer (61), which implies that BMI-1 is involved in malignant transformation.

Considering the aforementioned findings, BMI-1 is required for the maintenance of self-renewal, tumor initiation and prevention of inappropriate differentiation of CSCs. However, the molecular mechanisms underlying these biological processes remain unclear.

4. Signaling pathways of BMI-1 in the regulation of cancer and CSCs

Upstream signaling pathways. Notably, previous studies have implicated MYC in the regulation of the chromatin structure, which is reprogrammed in stem cells. MYC is able to modulate BMI-1 by adjusting the expression of the microRNA, miR-9, and long non-coding RNAs that are involved in polycomb-mediated gene silencing (27,62-65). Coskun *et al* (66) and Ke *et al* (67) demonstrated that the bFGF-SHP2-ERK-c-MYC-BMI-1 signaling pathway is critical for the self-renewal capacity of neural stem cells.

SALL4, a member of the *SALL* gene family, is one of the most important transcriptional regulators of stem cells. This gene is of particular interest to stem cell biologists, due to its association with the self-renewal of embryonic stem cells and HSCs. In normal HSCs and LSCs, *SALL4* is linked to *BMI-1* (68). Yang *et al* demonstrated that *BMI-1* is a direct target gene of SALL4 (69). The induction of SALL4 expression was demonstrated to be associated with increased levels of histone methylation (H3-K4 and H3-K79) in the *BMI-1* promoter (69).

Nuclear factor erythroid 2-related factor 2 (Nrf2) is an important nuclear transcription factor, which regulates antioxidant response element-containing genes. Zhu *et al* revealed that knockdown of Nrf2 inhibited the proliferation of glioma stem cells and significantly reduced the expression levels of BMI-1, Sox2 and cyclin E (70).

Mel-18 is one of the PcG proteins, which function as transcriptional repressors through epigenetic regulation, including histone modifications and DNA methylation, and their role in tumor development is critical. However, Mel-18 is a putative tumor suppressor in various human cancer tissues, unlike the *BMI-1* oncogene. Therefore, Mel-18 has been proposed as a novel negative regulator of BMI-1 as it inhibits breast cancer cell proliferation (71).

Downstream signaling pathways. Inactivation of BMI-1 is known to result in impaired stem cell self-renewal. Although the underlying mechanisms remain unclear, an important gene that is silenced by BMI-1 is *Ink4a/Arf*. This gene encodes the cell-cycle inhibitors, $p16^{Ink4a}$ and $p19^{Arf}$ (72), which regulate the activities of retinoblastoma (Rb) and p53, respectively. In addition, $p16^{Ink4a}$ and $p19^{Arf}$ restrain cell proliferation by partly overlapping signaling pathways that control the cell cycle, cell differentiation, senescence and survival (57,73,74). Chiba *et al* have indicated that repression of *Ink4a/Arf* is crucial in the oncogenic transformation of hepatic stem cells (75). A number of studies have also demonstrated that BMI-1 is able to promote stem cell self-renewal mainly by interfering with two signaling pathways, $p16^{Ink4a}$/Rb and Arf/p53 (20,76,77). Therefore, through the regulation of $p16^{Ink4a}$ and Arf, BMI-1 is involved in the malignant transformation and self-renewal of CSCs.

However, other BMI-1 targets may also exist, since the effects of BMI-1 on stem cells are not fully reversed by the deletion of the *Ink4a/Arf* gene (3). A previous study proposed a general BMI-1-mediated mechanism for the maintenance of CSCs and the prevention of inappropriate differentiation (3). Other studies have also demonstrated that the *Hox* gene is upregulated when *BMI-1* is inactivated (3,54,78-80). In addition, Biehs *et al* (3) have established that the deletion of *Ink4a/Arf* is able to only partially rescue *BMI-1*-null phenotypes and revealed that *Hox* expression is typically repressed by BMI-1. In addition, the authors demonstrated that the BMI-1-mediated repression of *Hox* genes preserves the undifferentiated state of stem cells (3).

Using chromatin immunoprecipitation assays, Song *et al* revealed that BMI-1 transcriptionally downregulated the expression of the tumor suppressor, phosphatase and tensin homolog (PTEN), in tumor cells through direct association with the PTEN locus (27). In addition, the authors observed that ablation of PTEN expression resulted in partial rescue of the migratory/invasive phenotype of BMI-1-silenced cells (27). Furthermore, Li *et al* established that inhibition of BMI-1 reduced the invasiveness of two HCC cell lines *in vitro* by upregulating PTEN expression (15). Angiogenesis is an essential process for sustaining tumor invasion and metastasis. A previous study demonstrated that BMI-1 is involved in glioma angiogenesis (81). Vlachostergios and Papandreou have revealed the involvement of the BMI-1/NF-κB/VEGF signaling pathway in the promotion of glioma cell-mediated migration of endothelial cells and neovascularization *in vitro* and *in vivo*, while NF-κB inhibition was demonstrated to reverse these effects (82). These results demonstrated that BMI-1 is involved in the invasiveness of cancer by regulating the expression of PTEN and the vascular endothelial growth factor. Finally, BMI-1 depletion enhances the chemosensitivity of HCC cells by inducing apoptosis and autophagy, which is associated with the PI3K/AKT signaling pathway (Fig. 1) (37).

5. Conclusions

A number of previous studies have demonstrated that BMI-1, a member of the PcG family, is associated with various types of human cancer and overexpression of BMI-1 plays a vital role in cancer cell proliferation, invasion/metastasis, chemosensitivity and patient survival. Furthermore, BMI-1 is involved in the maintenance of self-renewal, tumor initiation and prevention of inappropriate differentiation of CSCs by participating in multiple signaling pathways, suggesting that BMI-1 is important in maintaining the CSC properties. The presence of CSCs induces treatment failure of human tumors. Certain studies have indicated that silencing BMI-1 can reduce the malignant biological behavior of cancer, as well as the self-renewal and differentiation of CSCs. Therefore, BMI-1 is hypothesized to affect the malignant biological behavior of human tumors by regulating the self-renewal and differentiation of CSCs. In conclusion, BMI-1 may represent a promising target for the prevention and therapy of various human cancer types. Further understanding the molecular mechanism underlying the regulation of BMI-1 in human cancer and CSCs is of great clinical value.

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