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Concise Review: Role of BMI1, a Stem Cell Factor, in Cancer Recurrence and Chemoresistance: Preclinical and Clinical Evidences

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Key Words. BMI1 • Cancer stem cells • Cancer recurrence • Chemoresistance • Cancer

ABSTRACT

There is increasing evidence that a variety of cancers arise from transformation of normal stem cells to cancer stem cells (CSCs). CSCs are thought to sustain cancer progression, invasion, metastasis, and recurrence after therapy. Reports suggest that CSCs are highly resistant to conventional therapy. Emerging evidences show that the chemoresistance of CSCs are in part due to the activation of B cell-specific Moloney murine leukemia virus integration site 1 (BMI1), a stem cell factor, and a polycomb group family member. BMI1 is reported to regulate the proliferation activity of normal, stem, and progenitor cells. BMI1 plays a role in cell cycle, cell immortalization, and senescence. Numerous studies demonstrate that BMI1, which is upregulated in a variety of cancers, has a positive correlation with clinical grade/stage and poor prognosis. Although evidences are in support of the role of BMI1 as a factor in chemoresistance displayed by CSCs, its mechanism of action is not fully understood. In this review, we provide summary of evidences (with mechanism of action established) suggesting the significance of BMI1 in chemoresistance and recurrence of CSCs. STEM CELLS *2012; 30:372–378*

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

Traditional cancer therapies typically target the rapidly dividing tumor cells, however, some cells of the tumor are spared [1–3]. These spared tumor cells which are reported to be present within many tumor types exhibit the potential to regenerate and are called cancer stem cells (CSCs) [1–5]. This may explain the clinical scenario in which a tumor has an apparent volumetric reduction, however, is subsequently followed by local recurrence. While debate continues as to the precise identity and function of CSCs, there is general agreement that CSCs display increased chemoresistance and radioresistance [1-3, 6]. Therefore, understanding the biology of chemoresistance potential of CSCs may contribute to our understanding of tumor biology and would have far-reaching clinical implications. Although several molecules have been reported to confer chemoresistance to CSCs, much is not known whether stem cell factors play a role in chemoresistance of tumor cells including CSCs.

There is increasing evidence that polycomb group (PcG) proteins (discovered in *Drosophila* as epigenetic gene silencers) play a crucial role in cancer development and recurrence. PcG of proteins is composed of two multimeric protein complexes, that is, the polycomb repressive complex 1 (PRC1) and the polycomb repressive complex 2 (PRC2) [7]. The PRC1 complex includes B cell-specific Moloney murine leukemia virus integration site 1 (BMI1), Mel-18, Mph1/Rae28, M33, Scmh1, and Ring 2, while the PRC2 complex includes Eed, EzH, Suz12, and YY1 [7]. BMI1 is reported to play an important role in self-renewal of stem cells and is associated with a number of human malignancies [2, 5, 8-10]. Recent studies suggest that BMI1 is involved in the initiation of cancer, and targeting BMI1 by gene therapy abolishes chemoresistance in tumor cells [2, 3]. In this review, we summarized (a) the evidences supporting the role of BMI1 in cancer recurrence and chemoresistance, (b) the mechanisms underlying, and (c) the potential approaches that could be used to target BMI1 for cancer therapy.

GENE AND PROTEIN STRUCTURE OF BMI1

Human *BMI1* gene localizes on short arm of chromosome 10 (10p11.23), which comprises 10 exons and 9 introns. The gene encodes a cDNA of approximately 3.4 kb length and a 36.8 kDa protein consisting of 326 amino acids, whereas mouse *Bmi1* gene encodes a protein of 45–47 kDa [2, 5]. With respect to amino acid sequence, a high degree of homology is found between human BMI1 and murine Bmi1 that was the first member of the PcG gene family identified in mammals. BMI1 protein contains a conserved ring finger domain in its N terminal end and a central helix-turn-helix-turn-

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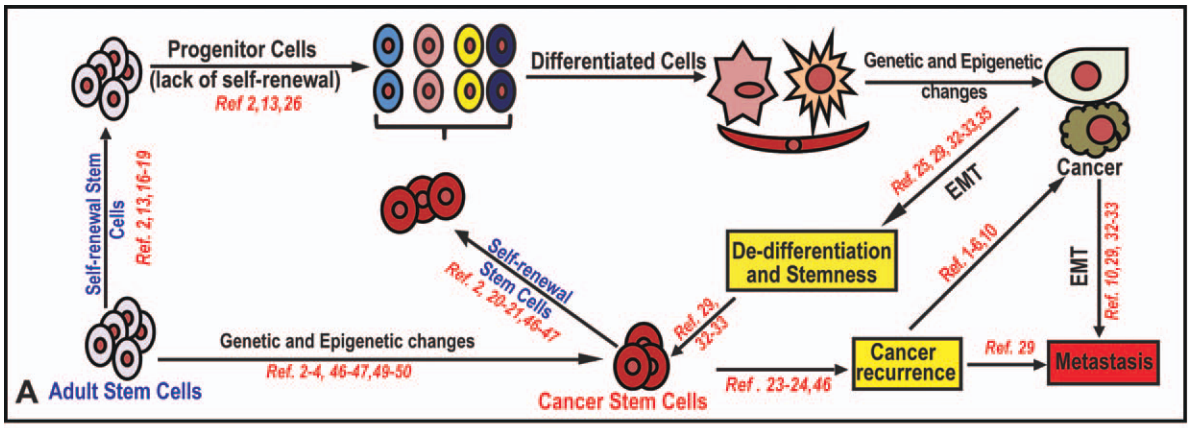

Table showing correlation of BMI1 expression with chemoresistance in different cancer types

Phenotype	Model	Model species	BMI1 status	Therapeutic agents	Function of the therapeutic agents	Chemoresistance	References
Prostate cancer	LNCaP & Du-145	Human	Overexpression	Docetaxel	Pro-apoptotic & anti-proliferative	Yes	3
Pancreatic cancer	Panc-1 (CD44+ cells)	Human	Overexpression	Gemcitabine	Pro-apoptotic & anti-proliferative	Yes	6
Squamous cell carcinoma	SCC-13	Human	Overexpression	EGCG	Pro-apoptotic & anti-proliferative	Yes	11
Normal cell	Keratinocytes	Human	Overexpression	Okadaic acid	Pro-apoptotic	Yes	12
Ovarian	Cancer Stem Cells	Human	Overexpression	Cisplatin and Paclitaxel	Pro-apoptotic & anti-proliferative	Yes	23
Ovarian cancer	A-2780, OCCAR-5 OV-202, OV-167, and CP-70	Human	Overexpression	Cisplatin	Pro-apoptotic & anti-proliferative	Yes	37
Glioma cells	U87MG, U251MG SNB19	Human	Overexpression	Doxorubicin & BCNU	Pro-apoptotic & anti-proliferative	Yes	38
Ovarian cancer	CP-20 mouse model	Mouse	Silenced	Cisplatin	Pro-apoptotic & anti-proliferative	No	37

B

Figure 1. Role of BMI1 in malignant transformation of stem cells into cancer stem cells and chemoresistance. **(A):** Pictorial diagram representing role of BMI1 during cellular events associated with the malignant transformation of stem or differentiated cells into cancer stem cells. The numerical number given on each arrow within the figure represents the reference number cited in the manuscript. **(B):** Table showing correlation of BMI1 expression with chemoresistance in different cancer types assessed in in vitro and in vivo models. Abbreviations: BCNU, Bis-chloroethylnitrosourea; BMI1, B-cell-specific Moloney murine leukemia virus integration site 1; EGCG, epigallocatechin-3-gallate; EMT, epithelial–mesenchymal transition.

helix-turn motif (H-T-H-T), which is essential for inducing telomerase activity [2, 5]. BMI1 contains two nuclear localization signals, KRRR and KRMK.

BMI1 has a ubiquitous pattern of expression in almost all tissues and its expression levels are observed to be high in the brain, esophagus, salivary gland, thymus, kidney, lungs, gonads, placenta, blood, and bone marrow [5]. Balasubramanian et al. [11] has reported the expression of BMI1 in basal and suprabasal keratinocytes. BMI1 is reported to be present in epidermal layers but not in dermis [12].

BMI1 in Normal Stem Cells

Stem cells are of two types (a) embryonic stem cells (ESCs) and (b) adult stem cells (ASCs). ESCs are pluripotent stem cells capable of developing into different cells, however, ASCs maintain and repair their resident tissues in adult organisms. Thus, self-renewal, differentiation, and prevention of senescence of ASCs are critical for tissue homeostasis. BMI1 plays crucial role for self-renewal and differentiation of leukemic stem and progenitor cells [13 and references therein]. BMI1 has also been reported to prevent senescence and immortalize cells through the activation of telomerase [8, 14]. It is reported that Bmi1 plays a crucial role during proliferation of normal stem and progenitor cells derived from fetal liver [13]. Hosen et al. [15] showed that the expression of BMI1 is high in primitive hematopoietic stem cells (HSCs) and is decreased when HSCs are differentiated into a particular lineage. The self-renewal and maintenance of HSCs and neural stem cells (NSCs) were reported to depend on the level of BMI1 protein [8, 16]. These studies suggest a strong correlation of BMI1 with the differentiation and growth of stem cells [15, 16]. BMI1 is reported to play a crucial role during the self-renewal and maintenance of prostate, intestinal, lung epithelial and bronchioalveolar stem cells [17–19].

BMI1 and CSCs

Over the past two decades, evidence has emerged to suggest that cancer could be considered as a stem cell disease and molecular mechanisms governing stem cell self-renewal are subverted during tumorigenesis to maintain cancerous growth (Fig. 1A, 1B) [2]. CSCs were first identified from the blood of patients with acute myeloid leukemia (AML) by Lapidot et al. in 1994 [4]. The CSC theory assumes that both primary and metastatic tumors develop from a small population of cancer cells possessing the characteristics of self-renewal and multipotency and are responsible for initiation and maintenance of tumors (Fig. 1A) [20, 21]. Additionally, CSCs can give rise to wide variety of differentiated cancer cells that comprise the

bulk of the tumor and provide the basis of tumor heterogeneity [20–22]. However, the stability of the CSC phenotype has not yet been completely understood [22]. Published reports suggest that CSCs are responsible for cancer recurrence after therapy and that this property of CSCs is attributed to the activation of different molecules including BMI1 [23–25].

BMI1 expression is frequently upregulated in various types of human cancers [1-2, 23-27]. There are reports that BMI1 acting as an epigenetic modifier protein is involved in the maintenance of CSCs [23, 25]. It is noteworthy that BMI1 is highly enriched in CSCs, however, all BMI1-expressing cells are not CSCs. BMI1 is coexpressed with other stem cell markers (CD133 and CD44) in CSCs [1, 6, 7, 23-26].

Aberrant BMI1 expression is reported in many CSC population. Bmi1 has been reported to be highly expressed in $CD133^+$ murine liver CSCs and play a role in maintenance of hepatic stem/progenitor cells [26]. Zhang et al. [23] observed that ovarian CSCs exhibit higher BMI1 levels than differentiated tumor cells. BMI1 has been shown to be involved in the regulation of CSCs from type-I neuroblastoma [9]. BMI1 was reported to regulate the self-renewal of CSCs by controlling their specific lineage commitment in an expression-dependent manner [9]. AML is a type of cancer in which the bone marrow makes abnormal myeloblasts, red blood cells, and platelets [13]. The proliferation of leukemic stem cells (LSCs) in a mouse model of AML was reported to be promoted by Bmi1 [13]. Bmi1-expressing LSCs were able to induce leukemia when transplanted into irradiated mice, whereas *Bmi1*-null LSCs exhibited limited proliferative potential and were unable to induce disease [13]. This study suggested the critical role of Bmi1 in proliferation of CSCs in leukemia [13]. Medulloblastoma is a type of brain tumor that originates from progenitor cells residing in the external cerebellum. Role of BMI1 in medulloblastoma can be ascertained from the fact that knockdown of *BMI1* in progenitor cells caused suppression in the proliferation and development of disease [27]. These studies suggest that the presence of BMI1 plays an important role in the proliferation of stem cells involved in tumorigenesis.

Different cell types that express BMI1 (such as endothelial cells, mesenchymal stem cells [MSCs], along with CSCs) reside within the tumor microenvironment [20, 28, 29]. The communication between CSCs and other cell types within tumor microenvironment plays an important role in invasion and therapeutic resistance [20, 28, 29]. Each established cell population within tumor exhibit a unique molecular marker that identifies and distinguishes it from other cell types [20-21, 28]. For example, MSCs express aldehyde dehydrogenase 1 (ALDH1) among breast CSCs population [20]. However, there is possibility that unique parental marker/trait still persists in cells that are in a stage of phenotypic transition such as mesenchymal transition [20, 28]. This also holds true with CSCs. A comprehensive discussion on this topic is beyond the scope of the theme of current manuscript.

BMI1, Self-Renewal and Cell Cycle

BMI1 controls self-renewal and cell cycle by regulating the tumor suppressor proteins p16INK4a and p14ARF in cells [8, 14]. BMI1 has been shown to activate the self-renewal ability of NSCs [16]. Recently, Dong et al. [30] demonstrated that loss of BMI1 in endometrial cancer cells reduces expression of stemness genes SOX-2 and KLF4 suggesting that BMI1 is required for regulation of stemness of this cell type.

The p16INK4a protein inhibits binding of Cyclin D to CDK4/6, resulting in the (a) suppression of retinoblastoma (RB) activity and (b) induction of cell cycle arrest [8, 31]. p19Arf (a homolog of human p14ARF) induces p53 and causes cell cycle arrest [8, 16, 31] (Fig. 2A, 2B). BMI1 promotes cell proliferation by suppressing p16INK4A/RB and/or p14ARF/MDM2/p53 tumor suppressor pathways [31]. The absence of BMI1 is reported to relieve the repression of the *INK4a* and resulting in the expression of p16INK4a and p14ARF. Data accumulated so far suggest that BMI1 abolishes cell cycle check points p16/p14 in various cell types (which exhibit different rates of growth/cell cycle kinetics) [7]. We speculate that this holds true for CSCs too. However, the possibility is that BMI1 could not be a sole factor deciding the fate of cells. Although BMI1 is present in CSCs, there is possibility that different subpopulation among CSCs (such as quiescent CSCs) exhibit different rate of growth. This could be possible due to the presence of factors other than BMI1 [18].

BMI1, Epithelial–Mesenchymal Transition and CSCs

The epithelial–mesenchymal transition (EMT) is a key developmental program that is often activated during cancer development [32, 33]. The occurrence of EMT in cancer cells may lead to the number of changes including loss of polarity and epithelial cell markers, loss of contact inhibition, reorganization of the actin cytoskeleton, remodeling of extracellular matrix components, gain of mesenchymal phenotypes along with genetic/epigenetic modifications of different genes, and persistent activation of different growth factors [32, 33]. Published reports suggest a direct link between the EMT and the gain of MSC-like properties [32, 33]. Raimondi et al. [33] reported that the induction of EMT program does not only allow cancer cells to disseminate from the primary tumor but also promotes their self-renewal capability. The sustained stimulation of growth factors may result in an upregulation of diverse gene products in CSCs and their differentiated progenies during the EMT process [32, 33]. Experimental evidence revealed that EMT is involved in anticancer drug resistance [32]. Thus, identification of molecular events that regulate EMT could lead to the development of a new therapeutic approach to suppress growth of CSCs. Song et al. [25] demonstrated that ectopic expression of BMI1 in normal nasopharyngeal epithelial cells is sufficient to cause EMT. Furthermore, this study showed that BMI1 induces EMT by targeting the tumor suppressor PTEN [25]. This in vitro observation was consistent with a cohort of human biopsy samples where an inverse correlation between BMI1 and PTEN was observed [25]. Recently, Yang et al. [29] showed that BMI1 is essential for EMT during tumor development in head and neck cancer patients. This study showed that increased levels of BMI1 were correlated with the worst prognosis in patients with head and neck cancer [29]. The molecules which are frequently altered in cancer cells during the EMT process are E-cadherin, N-cadherin, Vimentin, Tenascin C, NF-κB, SLUG, TWIST, SNAIL, β-Catenin, and CXCR4 [32, 33]. Collectively, these molecules are thought to contribute to the metastatic phenotypes of CSCs and enhance resistance to radiotherapy and chemotherapy [32, 33]. It has been reported that normal human mammary epithelial cells adopt a mesenchymal phenotype and exhibit stem cell-like properties upon expression of SNAIL and TWIST [32]. TWIST is reported to inhibit the senescence inducer proteins (p16 and p21) and co-operates with activated rat sarcoma (RAS) to trigger EMT [32]. Induction of SLUG is known to suppress E-cadherin, which results in the promotion of EMT [34]. Interestingly, $CD133^+$ breast

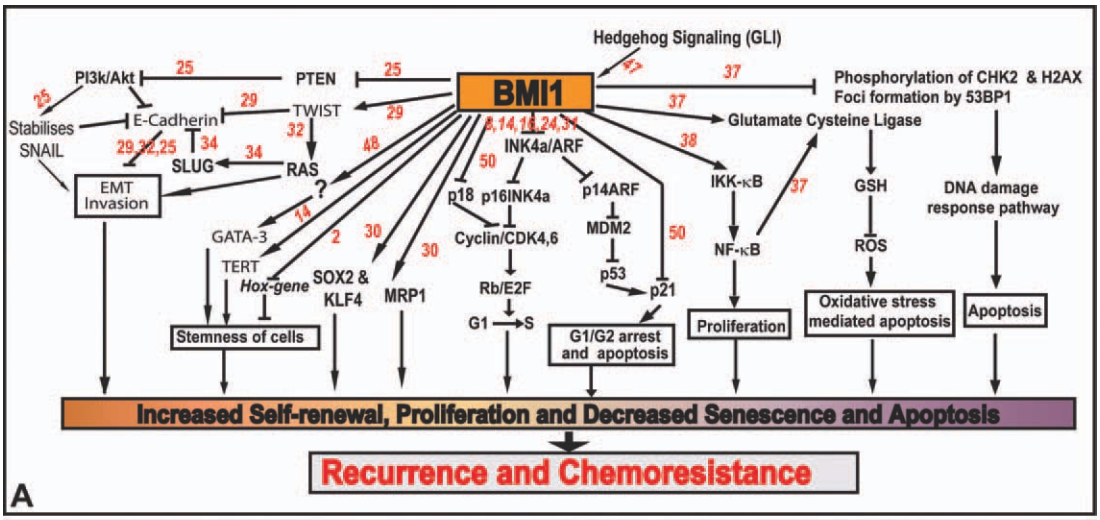

Table showing the published literature that formed the basis of model as represented in Fig. 2A

References	Reference number	References	Reference number
Cao et al., [2011]	2	Jacobs et al., [1999]	31
Park et al., [2004]	8	Thiery et al., [2009]	32
Dimiri et al., [2002]	14	Schmidt et al., [2005]	34
Molofsky et al., [2005]	16	Wang et al [2011]	37
Song et al., [2006]	24	Li et al., [2010]	38
Song et al., [2009]	25	Liu et al., [2006]	47
Yang et al., [2010]	29	Hosokawa et al., [2006]	48
Dong et al., [2011]	30	Facchino et al., [2011]	50

B

Figure 2. Role of BMI1 in cancer recurrence and chemoresistance. **(A):** Flowchart represents role of BMI1 and its interacting proteins during self-renewal, proliferation, and chemoresistance of cancer cells. **(B):** Table showing the published literature that formed the basis of model as represented in (A). The numerical number given on each arrow within the figure represents the reference number cited in the manuscript. ⊣ Represents inhibition and → represents activation. Abbreviations: BMI1, B-cell-specific Moloney murine leukemia virus integration site 1; EMT, epithelial–mesenchymal transition; GSH, reduced glutathione; IKK, IKB kinase; NF, nuclear factor; ROS, reactive oxygen species.

CSCs that express SLUG are also found to express high BMI1 [35]. BMI1 in co-operation with TWIST1 was reported to promote cancer dedifferentiation and metastasis [29]. Keeping in view that (a) EMT and stemness are interlinked processes, (b) EMT and stemness processes confer chemoresistance to tumor cells, and (c) BMI1 plays role in both EMT and stemness processes, the importance of BMI1 in chemoresistance as a major factor is further strengthened.

BMI1 and Chemoresistance: Preclinical Evidences

The inability of tumor cells to undergo apoptosis in response to chemotherapy poses a selective advantage for tumor progression, metastasis, and resistance to therapy. BMI1 has been reported to be associated with the protection of tumor cells from apoptosis (Fig. 1B). Cui et al. [9] showed that the ectopic expression of BMI1 rescues keratinocytes from stress-induced apoptosis. Bmi1 knockdown was observed to increase the apoptosis in lymphocytes in spleen and thymus in an animal model [36]. Zhang et al. [23] observed that ovarian CSCs exhibiting high BMI1 levels have increased resistance to Cisplatin and Paclitaxel. Crea et al. showed that BMI1 silencing significantly enhanced the antitumor efficiency of Docetaxel against prostate cancer cells. BMI1 (by modulating antioxidant machinery) was observed to allow prostate tumor cells to survive after chemotherapy [3]. Examination of clinical datasets revealed a positive correlation of BMI1 and antioxidant gene expression in patients exhibiting chemoresistance [3]. Recently, Wang et al. [37] reported that BMI1 is involved in chemoresistance of ovarian cancer cells, and targeting BMI1 by gene therapy sensitizes tumor cells to Cisplatin chemotherapy. Modulation of reduced glutathione (GSH) and CHK2 and H2AX molecules by BMI1 was reported as the underlying mechanism for chemoresistant behavior of ovarian tumor cells [37]. BMI1 silencing was found to reduce intracellular GSH levels and sensitize cancer cells to Cisplatin [37]. It is noteworthy that Cisplatin-induced apoptosis in such cell was found to be mediated by reactive oxygen species (ROS) generation [37]. Recent studies showed that overexpression of BMI1 rescues tumor cells from the apoptosis induced by Okadaic acid and Epigallocatechin-3-gallate, well-known apoptotic agents [11, 12]. Interestingly, artificial introduction of BMI1 in chemosensitive tumor cells was observed to confer chemoresistance in such cells [11]. Yin et al. [6] showed that $CD44^+/CD24^+$ pancreatic cancer cells expressing high levels of BMI1 exhibit chemoresistance to Gemcitabine treatment. Li et al. [38] reported that BMI1 by activating NF-κB significantly inhibits Doxorubicin-, BCNU-, and UV irradiation-induced apoptosis in glioma cells. Recently, we observed that the reduction of BMI1 protein levels by gene therapy abolishes chemoresistance in prostate carcinoma cells (Siddique et al., unpublished data). Taken together, these studies support the role BMI1 plays in conferring chemoresistance to tumor cells.

BMI1 and Chemoresistance: Clinical Evidences

The clinical significance of BMI1 in chemoresistance and its correlation with therapy failure in several cancer types has been established [5, 9, 10, 39–40]. BMI1 was found to be one of the key regulatory factors determining a cellular phenotype captured by the expression of a death-form-cancer signature in a broad spectrum of therapy-resistant cancers, including five epithelial (prostate, breast, lung, ovarian, and bladder cancers) and five nonepithelial (lymphoma, mesothelioma, medulloblastoma, glioma, and AML) malignancies [39]. Glinsky et al. [39] described a conserved BMI1-driven pathway of 11-gene signature which defines stemness of highly invasive tumors of multiple tissue origin and correlation with therapy failure. High level of BMI1 in tumors was reported to be positively correlated with poor prognosis in nasopharyngeal carcinoma patients [24]. BMI1 was identified as predictive factor for overall survival in patients with head and neck squamous cell carcinomas (HNSCC) [41]. BMI1 levels were observed to be increased in 79% of HNSCC patients, and a positive correlation was observed between BMI1 levels and lack of response to radiotherapy or chemotherapy [41]. Van Kemenade et al. [42] reported that poor outcome and aggressive tumor behavior were correlated with high BMI1 levels in patients with non-Hodgkin B-cell lymphomas and nasal pharyngeal carcinoma. Li et al. [38] showed that BMI1 was upregulated in 93.9% glioma specimens from 297 patients. This study showed that BMI1 expression was inversely correlated with survival time of glioma patients and positively correlated with the poor prognosis of the disease [38]. Mihic-Probst et al. [10] studying 329 melanoma patients reported that high expression of BMI1 in 64% of primary and 71% metastatic melanoma was associated with clinical progress of the disease. Recent reports show a correlation between BMI1 levels and recurrence cum survival of disease in tongue cancer, oropharyngeal squamous cell cancer, and non-small cell lung cancer (NSCLC) patients [5, 43, 44]. Disease-free survival for stage I and II of NSCLC patients who had received adjuvant therapy was reported to be better in BMI1-negative patients than BMI1-positive counterparts [44]. We observed a stage-dependent increase in human prostatic tumors and decreased chemoresistance in cells exhibiting reduced BMI1 levels (Siddique et al., unpublished data). Collectively these studies also suggest that BMI1 might be applicable as predictive markers of therapy during the follow-up of patients undergoing chemotherapy.

Molecular Mechanisms of BMI1-Induced Chemoresistance

Chemoresistance has been reported to be caused by the aberration of several molecular pathways in tumor cells. CSCs have been shown to display chemoresistance through (a) modulation of DNA repair machinery, (b) ATP-binding cassette (ABC) multidrug resistance, (c) quiescence, and (d) upregulation of antiapoptotic genes [45]. Emerging evidences support the notion that BMI1 is an important molecule in the process of chemoresistance. However, the precise mechanism of BMI1 on the regulation of chemoresistance in tumor cells is not completely understood. As presented in Figure 2, BMI1 is reported to modulate several molecular pathways within the cells. BMI1 has been shown to induce its effect at epigenetic as well as genetic level [7, 13, 46]. It is believed that chromatin modifications induced by PcG proteins (including BMI1) create an obstacle to transcription factors and RNA polymerase binding [46]. BMI1 has been shown to modulate chromatin by (a) forming a complex with methylated Lys_{27} of H3 and (b) catalyzing the ubiquitinylation of histone H2A [7, 46]. The co-operation between the Eed complex (that modifies chromatin by recruiting histone deacetylases) and BMI1 complex leads to the silencing of target gene expression [7, 46]. BMI1 induces immortalization of cells by downregulating the p16INK4a and p14ARF [8, 16]. Huber et al. [5] reported a correlation between low expression of p16 and high expression of BMI1 in human cancer patients. It is reported that the cooperation of BMI1 with c-MYC results in induction of telomerase activity and downregulation of *INK4a*/ARF [36].

Sonic Hedgehog (SHH) pathway is reported to play a role in the self-renewal of breast stem/progenitor cells [47]. SHH-activated mammosphere formation is reported to be mediated by BMI1 [47]. BMI1 is reported to regulate intracellular GSH levels by modulating glutamate cystine ligase, which is also positively regulated by Nrf-1 and nuclear factor κB (NF-κB) [37]. It is noteworthy that BMI1 expression was reported to be positively associated with activity of Nrf-1 and NF-κB in glioma cells [38]. BMI1 is reported to occupy the *PTEN* locus and downregulates *PTEN* expression [25]. Occupancy of BMI1 on *PTEN* locus results in the activation of Phosphatidylinositol 3-kinases/protein kinase B (PI3K/AKT) pathway, stabilization of SNAIL, and downregulation of E-cadherin. BMI1 directly occupies the promoters of CDH1 (which encodes E-cadherin) and *INK4a* [25]. Lee et al. [12] showed that BMI1 influences cell proliferation by increasing the expression levels of cyclin-dependent Kinase 2, 4 (CDK2, CDK4), and Cylin D1. BMI1 is reported to regulate stability of GATA binding protein 3 (GATA3), a transcription factor that is involved in Th2 cell development and differentiation [48]. Recently, Dong et al. [30] demonstrated that loss of BMI1 in endometrial cancer cells reduces expression of drug resistance gene MRP1, suggesting that BMI1 is required for the drug resistance. Quiescent nature of CSCs represents an inherent mechanism that at least partially explains chemotherapy resistance and recurrence in post-therapy in cancer patients [18, 20, 30]. Recent study by Tian et al. [18] suggest that Bmi1 plays an important role in the maintenance and growth of quiescent cells. Bmi1-expressing quiescent cells were shown to contribute to the generation of epithelial cells of intestine [18]. It is noteworthy that this effect of BMI1 was observed under conditions when proliferative cells were not sufficient and BMI1 expressing-quiescent cells were found to grow into tissue [18].

BMI1: A Potential Target for Cancer Therapy

CSCs may be eliminated by selectively targeted therapies against BMI1 [49, 50] (Siddique et al., unpublished data). However, it would be much complex to selectively target CSCs without any harmful effects to normal stem cells because normal stem cells and CSCs share the same pathways to maintain their self-renewal capability. It appears that CSCs are more likely to be more dependent on certain putative pathways. In this context, Liu et al. showed that human BMI1 is critical for the short-term survival of cancer cells, and inhibition of BMI1 has minimal effect on the survival of normal cells. These findings provide a foundation for developing a cancer-specific therapy targeting BMI1 [49]. Recently, Facchino et al. showed that glioblastoma multiforme (GBM) stem cells acquire an oncogenic trait by BMI1 overexpression thus distinguishing CSCs from normal stem cells. This situation was observed to render GBM stem cells

more sensitive to BMI1 inhibition than normal stem cells [50]. Based on compelling evidences (which suggest the critical role of BMI1 in growth and proliferation), using BMI1 as a target for anticancer therapy seems an ideal option. Wang et al. successfully tested 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine nanoparticles carrying small inhibitory RNA (siRNA) to target BMI1 and reported an inhibition in the growth of chemoresistant ovarian tumors implanted in a xenograft mouse model [37]. This study showed that gene therapy-induced BMI1 silencing along with Cisplatin completely abrogated ovarian tumor growth [37].

We recently showed that targeted inhibition of BMI1 by adopting gene therapy approach resulted in the reduction in the invasive potential and tumorigenic potential of prostate cancer cells (Siddique et al., unpublished data). We have embarked upon a broad program aimed to evaluate the potential and usefulness of BMI1 as a molecular target for human cancers. We have developed specific BMI1 small molecule inhibitors (Siddique et al., unpublished data), which were observed to inhibit the proliferative potential of prostate, pancreatic and skin cancer cells (Siddique et al., unpublished data).

Conclusions

BMI1 has been reported to be associated with the progression, recurrence, and chemoresistance to the various types of cancer cells. Hence, it is of great clinical value to further understand the molecular mechanism underlying the regulation of BMI1 in CSCs and chemoresistance. This will not only help in understanding the role of BMI1 in the growth of CSCs and chemoresistance but will also provide insights for the establishment of new strategies and effective clinical therapies for the treatment of chemoresistant cancers. Taken together, these studies show that BMI1 has the potential to be developed as a target for therapeutic agents and small molecules efficiently targeting BMI1 offer an option as future anticancer drugs.

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Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflict of interest.

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