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Review

BMI1 in the heart: Novel functions beyond tumorigenesis

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ABSTRACT

The BMI1 protein, a member of the PRC1 family, is a well recognised transcriptional suppressor and has the capability of maintaining the self-renewal and proliferation of tissue-specific stem cells. Numerous studies have established that BMI1 is highly expressed in a variety of malignant cancers and serves as a key regulator in the tumorigenesis process. However, our understanding of BMI1 in terminally differentiated organs, such as the heart, is relatively nascent. Importantly, emerging data support that, beyond the tumor, BMI1 is also expressed in the heart tissue and indeed exerts profound effects in various cardiac pathological conditions. This review gives a summary of the novel functions of BMI1 in the heart, including BMI1-positive cardiac stem cells and BMI1-mediated signaling pathways, which are involved in the response to various cardiac pathological stimuli. Besides, we summarize the recent progress of BMI1 in some novel and rapidly developing cardiovascular therapies. Furtherly, we highlight the properties of BMI1, a therapeutic target proved effective in cancer treatment, as a promising target to alleviate cardiovascular diseases.
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1. Introduction

B cell-specific Moloney murine leukemia virus integration site 1 (BMI1), a component of the polycomb repressive complex 1 (PRC1), is recognized as a polycomb protein that prevents premature senescence and maintains the self-renewal capacity of stem cells [1]. The gene encoding BMI1 was first defined as an important oncogene which is essential in collaborating with Myc in the oncogenesis of lymphomas, hence its name [2]. The human Bmi1 gene is located on the short arm of chromosome 10 (10p13) and encodes a 37kDa protein which consists of 326 amino acids [3]. The analysis and comparison of Bmi1 nucleotide and the deduced amino acid sequence showed its considerable homology among mice, rats, and humans [4]. The encoded BMI1 is an evolutionarily highly conserved protein, whose functionality highly relied on several defined motifs, including N-terminal RING finger domain, a helix-turn-helix domain, C-terminal PEST (proline, glutamic acid, serine, and threonine) sequences, and nuclear localization signal (NLS) 1 and 2 [5,6]. BMI1 was found present in almost all kinds of tissues, and especially highly expressed in brain, kidney, gastrointestinal tract, placenta, thymus, parathyroid, salivary glands, gonads, and bone marrow [7]. In adult mammals, stem cells are a small number of cells resident in many tissues that contribute to both their self-renewal and differentiation into mature cells [8]. Documented studies have confirmed that BMI1 is a key regulator highly expressed in stem cells (including neural/intestinal/hematopoietic stem cells, etc.) and required for stem cell self-renewal [9]. In addition, increasing expression of BMI1 was detected in a number of tumoral tissues compared to their normal counterpart cell types, indicating BMI1 occupied an important position in tumorigenesis [7].

Since its discovery, BMI1 has been recognized as a multifunctional regulatory factor involved in various biological processes, especially tumorigenesis. Notably, the physiological function of BMI1 in sustaining stem cell self-renewal likely contributes to its critical roles in maintaining the self-renewal of cancer stem cells (CSCs), a small fraction of neoplastic cells residing in various cancers and relevant with cancer metastasis and relapse. There have been studies showing that BMI1-overexpression CSCs are highly tumorigenic and chemo-resistant, while strategies targeting these CSCs effectively overcome tumor metastasis and therapy resistance

Abbreviations: BMI1, B cell-specific Moloney murine leukemia virus integration site 1; CDKN2b, cyclin dependent kinase inhibitor 2b; CICs, cancer-initialing cells; Cited 2, CBP/p300 interacting transactivator with ED-rich tail 2; CM, cardiomyocyte; DDR, DNA damage response; DDM, Duchenne muscular dystrophy; EPC, endothelial progenitor cell; FACS, fluorescence-activated cell sorting; HF, heart failure; hMSC, human mesenchymal stem cell; hUCB-MSC, human umbilical cord blood-derived MSC; iCM, induced cardiomyocyte; iNOS, inducible nitric oxide synthase; MI, myocardial infarction; MMP-2, matrix metalloproteinase-2; MSC, mesenchymal stem cell; PHLPP, PH domain and leucine−rich repeat protein phosphatase; PRC1, polycomb repressive complex 1; RB, Retinoblastoma; ROS, reactive oxygen species; Shh, Sonic hedgehog; TERT, telomerase reverse transcriptase

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[10,11]. Consistently, growing studies have suggested that BMI1 is frequently overexpressed in many types of tumors (such as breast cancer, prostate cancer, hematologic malignancies, etc.) and exerts profound effects in oncogenesis, tumor growth, tumor metastasis and chemotherapy resistance [12,13]. Besides, several previously published meta-analysis have confirmed that BMI1 may serve as an effective prognostic biomarker for gastric cancer, non-small cell lung cancer, and some other solid tumors [14]. With its function being gradually uncovered, BMI1 has been regarded as a potential target for cancer treatment. The experimental reduction of BMI1, to some degree, displayed antitumor effects, characterized by increased tumor cell death, improved susceptibility to chemotherapy, reduced metastases, and better prognoses [10]. Since the discovery of novel small molecule BMI1 inhibitors in 2014, such as PTC-209, emerging researches have been investigating its efficacy in tumors through pre-clinical and clinical experiments, indicating that selective inhibition of BMI1 is promising for cancer treatment [15].

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. In the past decades, the genetic, epigenetic and environmental mechanisms of CVDs have been continually studied and updated [16]. Many investigations have revealed that several oncogenes serve as significant regulators in the development and progression of various cardiovascular diseases, including c-myc, notch, ras, c-fos, etc. [17–20]. Importantly, the synergistic or antagonistic roles of oncogenes in the regulation of tumor growth and cardiac compensative process may position them at the crossing between cancer and cardiovascular diseases [21]. Actually, emerging researches have demonstrated that BMI1 is expressed in the heart tissue. By performing fluorescence-activated cell sorting (FACS) analysis of non-cardiomyocytes (non-CMs) from TM-induced BMI1-YFP mice, researchers uncovered a BMI1-expressing cardiac progenitor cell (B-CPC) population, which were maintained throughout the murine lifespan [22]. In homeostasis, B-CPCs served as a significant contributor to all three main cardiac lineages. Lineage tracing analysis confirmed the presence of YFP^+ CMs from BMI1-YFP murine hearts (2–12 months), which suggested the potential role of B-CPCs in CM turnover; besides, the co-localization of YFP with CD31/von Willebrand factor (vWF)/smooth muscle actin (SMA) in cells lining the vessel lumen was also observed, indicating B-CPCs contributed to smooth muscle and endothelial lineages [22]. Further transcriptome analysis of B-CPCs isolated from healthy BMI1-YFP murine hearts revealed that B-CPCs were enriched in stemness-related genes; additionally, Ingenuity Pathway Analysis showed that upstream regulators in the B-CPC population were mainly related to stemness and heart development [23]. These results indicate that BMI1 is a key transcription factor controlling stemmness in cardiac homeostasis. A growing number of studies have also established that beyond tumorigenesis, BMI1 plays significant roles in cardiovascular pathology [24]. The known regulatory mechanisms of BMI1 in cancer research may expand our understanding of cardiac pathogeneses. Despite this, the modulations of BMI1 in cancers and cardiovascular diseases are not completely the same. In addition, therapeutic strategies that are suitable for cancer treatment may bring disasters to those also suffering from cardiovascular diseases, and vice versa. Thus, a comprehensive understanding of BMI1 function in the heart is necessary. This review summarizes the novel role of BMI1 in the heart (including BMI1-positive cardiac cells and BMI1-mediated signaling pathways in cardiovascular disorders), and highlights the therapeutic potentials of BMI1 for cardiovascular diseases. Importantly, we also briefly discuss the potential cardiovascular side effects of novel agents that specifically target BMI1 for cancer treatment.

2. Novel roles of BMI1 in the heart

Actually, most of the researches involving BMI1 to date is in the field of cancer, with a small number of studies focusing on BMI1 function in cardiac biology. In this section, based on the up-to-date reports, we give a narrative review on the potential role of BMI1 in the heart, especially emphasizing BMI1-positive cardiac stem cells and BMI1-related signaling pathways in the initiation and progression of cardiovascular disorders.

2.1. Localization of BMI1 in the heart

At the time when the BMI1 was first reported, it was confirmed that the heart tissue was one of the organs where Bmi1 mRNA was detected at a high level in mice and rats [4,5]. The heart is generally composed of CMs and non-CMs. In the past decades, with the emergence and development of various new technologies, the cellular localization of BMI1 protein in the heart has been gradually demonstrated. Data from immunohistochemical staining and western blot collectively revealed that BMI1 was expressed in the myocardium of sham mice, and a remarkable upregulation of BMI1 was observed in post-MI cardiac fibrosis [24]. RT-qPCR analysis showed that BMI1 was preferentially expressed in the YFP^+ non-CM fraction, and western blot analysis furtherly confirmed that little BMI1 protein was detected in CM fraction and YFP^- non-CM compartment [22]. Similarly, Herrero and coworkers used $Bmi1^{GFP/+}$ mice to analyze the expression of BMI1 in the heart tissue, and the FACS results showed that BMI1 was highly expressed in a subpopulation of non-CMs in adult mice, in contrast, low levels of BMI1 were detected in the adult myocytes [25].

During the development of early chick embryo, BMI1 was found to be expressed in various embryonic tissues that contain multipotent cell types, of particular note is the finding that BMI1 was present in the developing heart primordia [26]. As an important stem cell renewal regulator, BMI1 has been found highly expressed in intestinal, hematopoietic and neural stem cells and plays significant roles in tumorigenesis [27,28]. In order to precisely analyze the localization of BMI1 protein, Bmi1–GFP–knock–in mice were usually generated [29]. Importantly, emerging discoveries have described the expression of BMI1 in cardiac stem cells, which have the ability to differentiate into specialized cells in the heart [22,23,30]. Utilizing immunofluorescence localization, Yang and co-workers have also revealed the presence of BMI1 in cardiac fibroblasts [31]. Interestingly, immunofluorescence staining of heart sections from BMI1-YFP mice suggested that $BMI1^+$ non-CMs were distributed in variable-sized cell clusters. Of particular note is that $BMI1^+$ cells were preferentially located in perivascular and inter-sarcomeric sites [22].

2.2. $BMI1^+$cardiac stem cells in the modulation of cardiovascular disorders

The adult mammal heart, traditionally recognized as a terminally differentiated organ without generative capability, indeed has low CM turnover attributed to the cardiac resident stem cells [32]. It has recently been shown that BMI1 is required in the efficient renewal and activation of cardiac stem cells in the progression of some cardiovascular diseases, especially those accompanied by massive loss of CMs [23,30].

BMI1 is critical to maintain the primitive properties of the cardiac progenitor cells [33]. In BMI1-overexpressing cardiac progenitor cells, miR-300 was upregulated parallel to BMI1 and furtherly modulated BMI1 expression via a negative feedback loop; further exploration suggested that miR-300 acted as a potential downstream target of BMI1 and played important roles in controlling BMI1 levels, keeping pluripotent cell status, and preventing the differentiation of cardiac progenitor cells [33]. Meanwhile, $BMI1^+$ cardiac progenitor cells are enriched in stemness-related genes [22, 23]. Experimental data have demonstrated that Bmi1 GFP^{hi} cells enriched in cardiac stem/progenitor cells and were capable of differentiating into CM-like cells, endothelial cells and smooth muscle–like cells, and siRNA-induced BMI1 deficiency markedly repressed the proliferation and myocardial

differentiation of non-CMs; in myocardial infarction (MI)-treated murine models, BMI1 high-expressing cells increased approximately 2.7-folds in number within the infarction and border zones, where many CMs were observed around the $BMI1^{hi}$ clusters [30]. Although the lack of direct evidence, this study implied the possible contribution of BMI1 to post-MI cardiac repair. In addition, another study performed lineage-tracing analysis in adult BMI1-YFP mice to explore $BMI1^+$ cells-mediated response to MI. They reported that $BMI1^+$ cardiac progenitor cells displayed remarkable accumulation and activation following MI and contributed to a comparable number of *de novo* CMs, consolidating $BMI1^+$ cardiac progenitor cells as a promising effector to myocardial repair [23]. Similarly, based on genetic lineage tracing analysis, *in vivo* experiments demonstrated that in a MI murine model, $Bmi1^+$ progenitor cells resident in the heart underwent large proliferation and differentiation, resulting in *de novo* cardiac vasculature during post-MI ventricular remodeling, and depletion of these endothelial-related $BMI1^+$ cells led to impaired angiogenesis and reduced ejection fraction, ultimately resulting in an ischemic-dilated cardiac phenotype [25]. BMI1 were also expressed in the diabetic endothelial progenitor cells (EPCs) and participated in diabetic myocardial infarction, experimental data showed that BMI1 was capable of mediating the antiapoptotic role of Shh pathway via inhibiting p53, and the activation of Shh/BMI1/p53 axis in diabetic EPCs markedly reduced EPC apoptosis and ameliorated EPC dysfunction, ultimately rescuing the diabetic myocardium under hypoxia [34].

$BMI1^+$ cardiac cells also exert profound effects on the oxidative stress, a crucial factor in many cardiovascular diseases. It has been illustrated that cells lacking BMI1 exhibit mitochondrial dysfunction, the disturbance of reactive oxygen species (ROS) homeostasis, and the activation of DNA damage response (DDR) pathway; correspondingly, antioxidants or interruption of DDR pathway can rescue the deficiency of BMI1 [35]. BMI1 was also found present in the inner mitochondrial membrane, beyond its previously described nuclear localization, and participated in the direct modulation of mitochondrial bioenergetics; meanwhile, BMI1 deficiency resulted in reduced stability of mitochondrial RNA and increased ribonuclease activity of polynucleotide phosphorylase [36]. With regard to the cardiovascular field, Herrero and colleagues provided evidence on the contribution of BMI1 in the turnover of adult progenitor cells in response to cardiac oxidative stress [37]: in the cardiac steady-state, BMI1 mainly binds to the canonical cell fate-related DNA targets in cardiac progenitors; while in response to an accumulation of ROS triggered by oxidative stress, BMI1 delocalized from DNA canonical targets to the non-canonical ones and regulated the terminal differentiation of cardiac stem cells to CMs, and it has been observed that 25% of the CM-committed cells in adult mice are derived from $BMI1^+$ cardiac cells. This research suggested that low ROS microenvironment favors maintaining quiescence of the progenitor population in the heart, while $BMI1^+$ cardiac progenitors tend to differentiate in the high ROS microenvironment, which was elaborately regulated via a BMI1-dependent mechanism. Besides, the levels of ROS were greatly enhanced with aging. Researchers utilized $Bmi1^{GFP}$ and $Bmi1^{CreERT}$ mice to investigate cardiac damage-responsive $BMI1^+$ cells in age-related cardiac stress: in young mice (2-3-weeks-old), damage-responsive $BMI1^+$ cells were randomly distributed in the heart tissue, while in adult mice (4-months-old), BMI1-positive cells were sheltered in the perivascular regions, which was proved to act as a specialized microenvironment with low ROS levels [38]. Co-culturing cardiac damage-responsive $BMI1^+$ cells with endothelial cells demonstrated the crosstalk between the two cell types, which was driven by cell-to-cell interactions as well as endothelial-related soluble factors (including Ephrinb2/Ephb4 and Vegfa/Vegfr2 signaling pathways) [38]. Strikingly, this study gave evidence that manipulation of ROS-related signaling and/or vascular niche may be therapeutically effective in cardiac injuries.

In summary, these results provide evidence that BMI1 can be expressed by cardiac lineages and non-CMs in homeostasis. When stimulated by cardiac ischemia or oxidative stress, cardiac resident BMI1-expressing progenitor cells respond quickly and positively. Therefore, modeling with the data obtained in cancer models, manipulation of BMI1 may constitute an essential therapeutic strategy in cardiovascular disorders. However, the response of all cardiac populations to damage is variable with respect to modulation of BMI1 expression. All this complexity must be considered and discussed when BMI1 is considered for an eventual treatment target. MI, a clinical syndrome caused by acute atherothrombotic plaque disruption or an imbalance between the supply and demand of myocardial oxygen, is characterized by the massive loss of CMs and cardiac vasculature within a short time [39,40]. Regeneration of the infarcted CMs is a critical issue but, for the moment, non-solved. Interestingly, previous research in skeletal muscle has demonstrated that mild overexpression of BMI1 in the satellite cells (muscle stem cells) dramatically improved muscle strength and function in Duchenne muscular dystrophy (DMD) mice, indicating the potentials of BMI1 to sustain the satellite cell-driven muscle regeneration in the muscle-wasting conditions [41]. Herein, the stimulation of the endogenous $BMI1^+$ cardiac stem cells or exogenous supplement of BMI1 perhaps could counteract MI-induced dysfunction and structural abnormalities (Fig. 1). Meanwhile, how the $BMI1^+$ cardiac cells interact with other cardiac progenitor-like clusters in the cardiac steady-state as well as pathological conditions remains unclear, and further investigations are required for a better understanding of the characteristics and subpopulations of these BMI1-positive cells.

2.3. BMI1 signaling in the heart

As we all know, tumor growth is precisely regulated by abundant signaling molecules, which interact with each other and ultimately form complex and diverse signaling networks. More and more

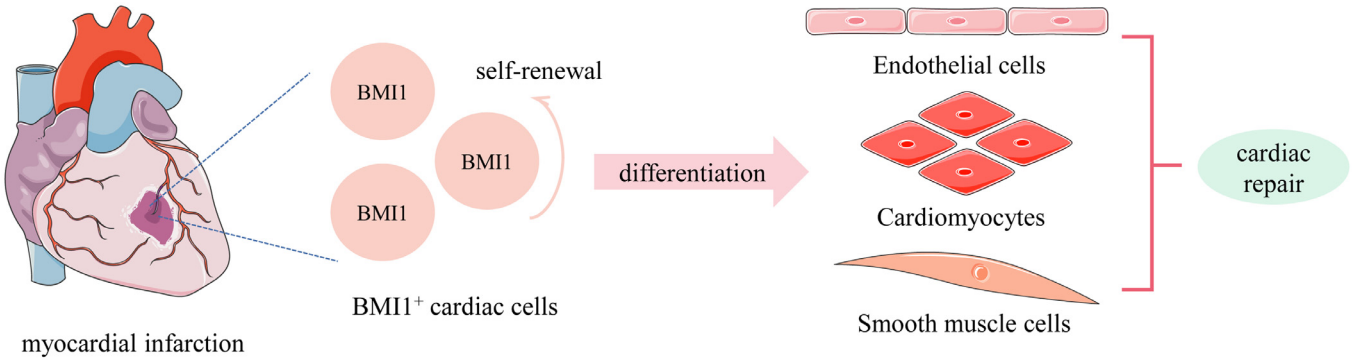

Fig. 1. The role of $BMI1^+$ cardiac cells in myocardial infarction. In response to myocardial infarction, $BMI1^+$ cardiac cells undergo extensive proliferation as well as differentiation into *de novo* cardiomyocytes and vasculature, which contribute to the regeneration of cardiac myocytes and cardiac angiogenesis. $BMI1^+$ cells play a positive role in sustaining cardiac structures and cardiac function post myocardial infarction.

studies have revealed that the signaling molecules that promote or prevent tumorigenesis may have potential regulatory effects in the cardiovascular system [42]. Some molecular and cellular pathways which link cancer and cardiovascular diseases include AMPK, PPAR-γ, Wnt signaling pathway, inflammation, oxidative stress, obesity, adipokines, etc. [42]. Several recent researches have uncovered that, BMI1, as a key regulatory suppressor first discovered in tumors, takes part in cardiac biology via signal transduction [24].

It is well established that the PTEN/PI3K/Akt signaling pathway acts as one possible mechanism by which BMI1 induces tumorigenesis [43]. Previous research has revealed that in nasopharyngeal carcinomas, BMI1 could directly bind to PTEN locus and subsequently downregulate the expression of PTEN, and then the PI3K/Akt/GSK3β signaling pathway was hyperactivated, ultimately resulting in the induction of epithelial−mesenchymal transition (EMT) and tumorigenesis [44]. It has also been shown that BMI1 was capable of inducing the invasion/metastasis of pancreatic cancer stem cells by activating PI3K/Akt pathway, which was negatively regulated by the tumor suppressor PTEN [45]. BMI1 and Akt were also involved in endometrial cancer, interestingly, BMI1 was downregulated and the low expression of BMI1 was intimately associated with the endometrial cancer progression, so as Akt [46]. In addition, it seemed that BMI1 influenced the level of Akt phosphorylation in endometrial cells by modulating PH domain and leucine−rich repeat protein phosphatase (PHLPP) expression [46]. These cancer models exemplifies the potential dual role of BMI1 (up- and downregulated) depending on the cancer contexts. Beyond tumorigenesis, BMI1-involved signaling pathways underlying cardiovascular disorders are being continuously investigated. Researches recently have demonstrated that BMI1 was highly expressed in the infarcted myocardium, and mostly importantly, the upregulated BMI1 exerted profibrotic effects on post-MI cardiac remodeling, which was achieved through promoting the proliferation and migration of fibroblasts as well as regulating PTEN-PI3K/Akt-mTOR signaling pathway [24]. In mice 4 weeks post MI, PTEN downregulation, PI3K upregulation, and increased phosphorylation of mTOR and Akt proteins were observed, which was in consistent with that in BMI1-overexpressing mice 4 weeks after intramyocardial injection. In addition, treatment with NVP-BEZ235, a dual PI3K/mTOR suppressor, remarkably reversed fibroblast proliferation and migration, consolidating the potentially profibrotic effects of PTEN-PI3K/Akt-mTOR pathway [24]. This study extended BMI1/PTEN/PI3K/Akt signaling in tumorigenesis and first demonstrated that BMI1 served as a significant profibrotic effector during the process of ischemia-induced cardiac remodeling. Thus, selective inhibition of BMI1 protein may ameliorate cardiac dysfunction and fibrosis post MI.

Cyclin dependent kinase inhibitor 2b (CDKN2b)-encoded p15 protein, a cyclin-dependent kinase inhibitor, participates in multiple solid tumors and hematological malignancies [47,48]. A latest study reported that CDKN2b/p15 was downregulated in both murine infarcted hearts and human failing hearts, and overexpression of CDKN2b remarkably ameliorated ischemia-induced cardiac dysfunction; mechanistically, BMI1, which was upregulated in the failing hearts, significantly downregulated p15 as well as enhanced the phosphorylation level of retinoblastoma (Rb) protein in cardiac fibroblasts, indicating critical roles of the BMI1-p15-Rb signaling in the post-MI remodeling [31]. Cited 2 (CBP/p300 interacting transactivator with ED-rich tail 2), which is associated with oncogenic cell transformation, is necessary for the normal expression of downstream BMI1 and Mel18 in primary mouse embryonic fibroblasts, and infection with Mel18- and BMI1- expressing retroviruses increased proliferation ability of mouse embryonic fibroblasts regardless of their Cited2 genotypes, indicating the potential roles of BMI1 in cell proliferation and may provide evidence for the possible roles of BMI1 in fibrogenesis, which is partly manipulated by fibroblast proliferation and migration [49]. Furthermore, BMI1 potentially exerts protective effects in the heart. Another recent research found that quercetin was effective in cardioprotection against doxorubicin-induced cardiotoxicity *in vivo* and *in vitro*, as evidenced by reduced apoptosis and oxidative stress, and improved mitochondrial function and cardiac systolic/diastolic function; notably, the cardioprotective effects of quercetin largely relied on the regulatory factor BMI1, which was decreased in doxorubicin-induced hearts while retained when pretreated with quercetin [50]. Similarly, the protective role of quercetin was also observed in a rat model of cardiopulmonary resuscitation, via reducing the expression of iNOS and MMP-2 as well as inducing the expression of BMI1 [51].

To sum up, these studies emphasized the potential regulatory roles of BMI1-related signaling pathways in some cardiac pathological conditions, especially ischemia-induced cardiac remodeling and doxorubicin-induced cardiotoxicity. The regulatory pathways in the heart and cancer may share some similarities, but some differences also exist (Table 1). Nevertheless, the current research on this filed is just the tip of the iceberg. Whether these BMI1 signaling pathways are involved in some other cardiovascular disorders are not completely clear. Furthermore, the crosstalk between these BMI1-mediated pathways in cancer and the heart still remains to be investigated.

3. BMI1 in novel cardiovascular therapies

Despite intensive efforts, our understanding of optimal therapies for various cardiovascular diseases, especially those with irreversible myocardial injury, still remains uncertain [52]. In recent years, some continuously improved therapeutic strategies for cardiovascular diseases include pharmacological treatment, implantable devices, cell therapy, etc. [53]. With regard to BMI1 protein, emerging studies have provided evidence that it plays a key role in the potential therapies for cardiovascular diseases, of particular note is that BMI1 participates in the modification of some cell types that could directly rescue the damaged myocardium.

3.1. Direct cardiac reprogramming

Direct cardiac reprogramming is a novel technique that can convert fibroblasts into induced cardiomyocytes (iCMs) under the inducement of some transcription factors, such as Gata4, Mef2C, Tbx5, etc. [54]. It is widely accepted that direct cardiac reprogramming creates new opportunities to regenerate a damaged heart [55]. However, the low efficiency and slow process of fibroblast-to-iCM conversion remain a major challenge, which may result from the unidentified epigenetic barriers [56].

Zhou et al [56] first utilized shRNA-based loss-of-function screen to investigate the roles of epigenetic regulators in direct cardiac reprogramming, surprisingly, they found that BMI1 was a critical epigenetic barrier to the iCM reprogramming, via directly binding to the regulatory regions of a series of cardiogenic factors and regulating their chromatin status; and the repression of BMI1 significantly enhanced active chromatin status at the cardiac loci and consequently promoted the generation of iCMs, highlighting the efficiency of BMI1 depletion to enhance and accelerate cardiac direct reprogramming. Pharmacological inhibition of BMI1 by PTC-209 for 24h also had the capability to accelerate the cardiac reprogramming of both adult and embryonic murine fibroblasts, interestingly, upon PTC-209 pre-treatment, a set of immune-related genes and inflammatory signaling pathways (including interleukins, cytokines, JAK/STAT3 and MAPK/ERK1/2 pathways, etc.) were downregulated, indicating their possible roles in holding back iCM reprogramming [57]. Similarly, another research revealed that the combination of four chemicals (BMI1 inhibitor PTC-209, TGF inhibitor A83-01, Mll1 inhibitor MM589 and IGF-1, termed as IMAP) coordinately improved reprogramming efficiency through specifically inhibiting C-C chemokine signaling pathway; administration of IMAP profoundly enhanced the expression of cardiac genes, sarcomere formation, and calcium flux, meanwhile, lineage tracing validated that

Table 1
The comparison of BMI1 signaling between cancer and cardiac biology.

Conditions	General effects	Models	Observations	Cell types	Regulatory pathways	Reference
Cancer	Tumorigenic	nasopharyngeal carcinoma	BMI1 upregulation induced epithelial-mesenchymal transition and promoted the development and progression of cancer.	nasopharyngeal epithelial cells	BMI1 binds to PTEN locus and subsequently activates the PI3K/Akt/GSK3β signaling pathway.	[44]
		pancreatic cancer	BMI1 was upregulated in pancreatic cancer stem cells and promoted their invasion and metastasis ability.	pancreatic cancer stem cells	BMI1 expression activates PI3K/AKT singing pathway by negative regulating PTEN.	[45]
	Anti-tumor	endometrial cancer	BMI1 was downregulated in endometrial cells/tissues, and patients with low BMI1 expression had a shorter overall survival than those with high BMI1 level.	endometrial cancer cells	BMI1 impacts on Akt phosphorylation level by regulating the expression of PHLPP.	[46]
Cardiac homeostasis	Cardioprotective	healthy hearts	B-CPCs served as a significant contributor to all three main cardiac lineages, including cardiomyocytes, smooth muscle and endothelial cells.	cardiac progenitor cells	B-CPCs are enriched in stemness-related genes, and their upstream regulators are related to stemness and heart development.	[22,23]
Cardiac disorders	Cardioprotective	myocardial infarction	BMI1 GFP^{hi} cells increased approximately 2.7-folds in number within the infarction and border zones, and many CMs were observed around the clusters of $BMI1^{hi}$ cells.	cardiac stem/progenitor cells	*In vitro* data suggest that the BMI1 GFP^{hi} cells could differentiate into SMM^{+} smooth muscle−like cells and TnT^{+} CM-like cells.	[30]
		myocardial infarction	$BMI1^{+}$ cardiac progenitor cells were conductive to cardiac repair following MI.	cardiac progenitor cells	BMI1-derived cells undergo proliferative activation shortly after MI and are involved in new CM generation.	[23]
		myocardial infarction	$BMI1^{+}$ progenitor cells contributed to *de novo* cardiac vasculature during post-MI ventricular remodeling, while depletion of these cells impaired cardiac angiogenesis and function.	cardiac progenitor cells	$BMI1^{+}$ progenitor cells are a relevant source of cardiac endothelial cells after MI.	[25]
		diabetic myocardial infarction	BMI1 contributed to reduced EPC apoptosis and improved EPC function, eventually rescuing diabetic myocardium under hypoxia.	endothelial progenitor cells	BMI1 mediates the benefits of the Shh pathway by inhibiting p53 in diabetic EPCs.	[34]
		cardiac oxidative stress	High levels of ROS enforced $BMI1^{+}$ cardiac progenitor differentiation. Cardiac $BMI1^{+}$ cells made up 25% of the CM-committed cells, which had the highest ROS levels of all adult cardiac progenitor cells.	cardiac progenitor cells	BMI1 delocalized from DNA canonical targets to the non-canonical ones and regulated the terminal differentiation of cardiac stem cells to CMs.	[37]
		aging	In young mice, damage-responsive $BMI1^{+}$ cells were randomly distributed in the heart tissue, while in adult mice, $BMI1^{+}$ cells were sheltered in the perivascular regions.	cardiac progenitor cells	Oxidative stress acted as a limiting factor of cardiac regenerative capacity, and reduced ROS levels disengaged $BMI1^{+}$ DR-cells from the vasculature.	[38]
	Pro-fibrotic	post-ischemia cardiac remodeling	BMI1 was upregulated in the infarcted myocardium and exerted profibrotic effects in post-MI cardiac remodeling.	cardiac fibroblasts	Promoting fibroblast proliferation and migration, and activating PTEN/PI3K/Akt-mTOR signaling pathway	[24]
		post-ischemia cardiac remodeling	BMI1 was upregulated in the failing hearts and contributed to ischemia-induced cardiac fibrosis and heart failure.	cardiac fibroblasts	Downregulating p15 and enhancing the phosphorylation level of Rb protein	[31]

the reprogrammed iCMs originated from fibroblasts instead of other lineages [58].

In conclusion, BMI1 has been identified as an important epigenetic barrier for direct cardiac reprogramming, thus removing BMI1 from human fibroblasts may serve as a promising strategy to improve the generation of human iCMs and repair the injured hearts with massive loss of CMs. However, most of the current reports about direct cardiac reprogramming are performed in mice, and the research on reprogramming of human fibroblasts is lacking [59]. Besides, a better understanding of the transcription factor networks as well as the basic signaling pathways is required for its further application into human therapies [60]. A very recent study has successfully uncovered previously unrecognized cellular and molecular dynamics of human fibroblast reprogramming by performing single-cell RNA sequencing, which paves way for the further exploration and clinical translation of cardiac reprogramming [61]. Furthermore, it is essential to focus on how to enhance the efficiency of cardiac reprogramming. The combined use of BMI1 inhibitors and iCM reprogramming boosters theoretically may bring benefits, but the combination is extremely complex and the effect varies, so screening for the optimal combination is a hard but necessary process, and further investigations are also required to reveal the safety and efficacy.

3.2. Cell therapies

Unlike other tissues, the heart tissue has a limited propensity to repair itself after injury. Cell-based therapies have been attempted to restore cardiac function in the severely damaged heart in preclinical (animal) models as well as clinical investigations [62,63]. Many kinds of cell types are useful sources for transplantation, such as bone marrow-derived mononuclear cells, cardiac stem cells, mesenchymal stem cells (MSCs), etc. [64]. Promisingly, BMI1 has been confirmed as a key modulator in stem cell biology and may be an essential target for promoting cell therapies in cardiovascular diseases [65].

MSCs are mesoderm-derived multipotent cells that have the capability of self-renewing and differentiating into diverse mesenchymal tissues such as muscle, bone, cartilage, fat, etc. [66]. Notably, *in vitro* experiments supported that MSCs were able to transdifferentiate into functional CMs [67,68]. These properties lay the foundation for the widespread application of MSC-based therapies in diseased hearts [69]. Human mesenchymal stem cells (hMSCs) transduced with BMI1, E6, E7, and telomerase reverse transcriptase (TERT) exhibited extended life span, and *in vitro* experiments demonstrated that although with low efficiency, these long-lifespan hMSCs treated by 5-azacytidine and cultured with fetal CMs were able to differentiate into CMs, which were distinguished by their morphology, electrophysiologic features and the expression of CM-specific genes [70]. This research provided an alternative strategy to prepare abundant MSCs for cell therapy with enhanced efficiency. Human umbilical cord blood-derived MSCs (hUCB-MSCs) are a promising source for clinical therapies to alleviate inflammatory response [71]. Researchers have found that BMI1 was upregulated in hypoxia-cultured hUCB-MSCs and acted as an intrinsic regulator of MSC senescence and immunomodulation; mechanistically, BMI1 directly suppressed the expression of MKP-1/DUSP1 via binding with DUSP1 promoter and subsequently contributed to the upregulation of phosphorylated p38/COX-2/PGE2 pathway, ultimately enhancing the immunomodulatory and proliferative properties of hUCB-MSCs [72]. Besides, transduce of BMI1/human telomerase reverse transcriptase (hTERT) contributed to the immortalization of primary neonatal rat CMs, which acquired the ability to proliferate for over six months of culture [73]. These immortalized cells were characterized by the expression of cardiac markers as well as the morphological features of dedifferentiation. Herein, the efficiency of the BMI1-mediated cell immortalization sheds light on the controllable cell expansion and potential application of cell therapy.

In the past decades, exciting scientific progress on cell therapies has been witnessed in preclinical animal models of MI [74]. However, embarrassing results from numerous clinical trials indicate that great challenges still exist [75]. Notably, available solutions to barriers are emerging in recent years [75], which may revitalize this field in the future and potentially promote the application of BMI1, a key regulator, in cell-based therapies for injured hearts. Under the inducement of BMI1 along with other epigenetic regulators, hMSCs exhibited favorable features conductive to the generation of *de novo* CMs. These observations may provide future possibilities to expand BMI1 to clinical use [76].

4. Novel small molecule BMI1 inhibitors: promising drugs in the near future

Ample studies have confirmed that BMI1 depletion mediated by selective small molecule BMI1 inhibitors represents an attractive therapeutic strategy for various cancers. PTC-209, the first generation of small molecule suppressor of BMI1, was first described by Kreso and colleagues: they found that intra-tumor administration of PTC-209 could suppress the self-renewal capability of colorectal cancer-initialing cells (CICs), resulting in massive loss of CICs and impairment of tumor growth [15]. Subsequently, numerous preclinical studies have suggested that treatment with PTC-209 significantly impaired tumor overgrowth and reduced drug resistance, and the combined use of PTC-209 and traditional anti-tumor agents strikingly led to better therapeutic effects [77–80]. PTC-028, a second generation BMI1 inhibitor, possesses optimized pharmaceutical properties [81]. The differences between PTC-209 and PTC-028 lie on their regulatory mechanisms, rates of BMI1 depletion, cellular ATP decrease, mitochondrial ROS generation, as well as their administration route and dosage [81]. *In vivo* and *in vitro* experimental data have revealed that PTC-028 remarkably inhibited the self-renewal capability of tumor cells and strikingly reduced tumor burden in the local and metastatic regions [82,83]. PTC-596 is another commonly used small molecule BMI1 inhibitor. PTC-596 acts as a cell-permeable small molecule which can induce the degradation of BMI1 protein at nanomoles [84]. Documented research has demonstrated that PTC-596 contributed to the massive death of $CD34^{+}CD38^{-}$ acute myeloid leukemia (AML) stem/progenitor cells but had no effects on the normal hematopoietic cells, indicating the highly selective properties of PTC-596 [84]. Up to now, only PTC-596 has entered Phase 1 clinical trial (NCT02404480), in which patients diagnosed with advanced solid tumors were enrolled. Besides, another Phase 1b clinical trial was initiated in 2018 in order to study PTC-596 plus radiotherapy in pediatric high-grade glioma (NCT03605550). Some other early phase clinical trials examining the effects of PTC-596 in solid tumors include NCT03761095 and NCT03206645.

To sum up, these findings highlight that BMI1 represents a feasible and viable therapeutic target against solid tumors and hematological malignancies. PTC-209, PTC-028, and PTC-596, which are novel and selective small molecule BMI1 inhibitors, have great translational potentials (Table 2). In the current studies, small molecule BMI1 inhibitors are mainly used in the treatment of cancers, where BMI1 protein is significantly overexpressed and highly associated with the prognosis of patients. However, till now, there exist no studies investigating the application of small molecule BMI1 inhibitors in cardiovascular disorders. Thus, further preclinical and clinical studies are required to demonstrate the cardiovascular effects of BMI1 suppressors. In view of their highly selective properties approved in cancer research, small molecule suppressors of BMI1 may act as a novel and effective treatment for certain cardiovascular diseases overexpressing BMI1. However, in view of the cell type-specific roles of BMI1 in response to pathological stimuli in cardiac tissues, it should be considered cautiously to use systemic BMI1 blockers.

Table 2
Administration of small molecule BMI1 inhibitors for cancer treatment.

Small molecule BMI1 inhibitor	Cancer type	Outcomes	Reference
PTC-209	Colorectal cancer	Intra-tumor administration of PTC-209 could suppress the self-renewal capability of colorectal cancer-initialing cells (CICs), resulting in massive loss of CICs along with impairment of tumor growth	[15]
	Ovarian cancer	PTC-209 induces nonapoptotic, caspase-independent autophagic cell death	[77]
	Multiple myeloma	PTC-209 remarkably decreased viable myeloma cell numbers, induced a G1 cell cycle arrest, promoted apoptosis and displayed synergistic activity with carfilzomib and pomalidomide	[79]
	Head neck squamous cell carcinoma	PTC-209 treatment impaired cell proliferation, increased cell apoptosis and chemosensitivity to 5-FU and cisplatin, and reduced colony formation, tumorsphere formation and tumor growth	[78]
	Head neck squamous cell carcinoma	Combination treatment of anti-PD1 and PTC-209 effectively inhibited metastatic tumor growth and prevent tumor relapse.	[80]
PTC-028	Ovarian cancer	PTC-028 treatment selectively inhibited cancer cells in clonal growth and viability assays, but had no effects on normal cells, PTC-028 also showed significant anti-tumor activity comparable with the standard cisplatin/paclitaxel therapy.	[81]
	Multiple myeloma	Bmi1 modulators induced mitotic arrest and subsequently resulted in the apoptosis of myeloma cells.	[82]
	Medulloblastoma	Administration of PTC-028 significantly reduced tumor burden in both local and metastatic compartments, PTC-028 also reduced medulloblastoma relapse.	[83]
PTC-596	Acute myeloid leukemia	PTC596 induced p53-independent mitochondrial apoptosis, and *in vivo* experimental data showed that PTC-596 displayed anti-leukemia activity, along with impaired leukemia cell growth and sparing normal hematopoietic cells.	[84]
	Glioblastoma multiforme	PTC-596 impaired glioblastoma multiforme colony growth and cancer stem cell self-renewal, extending median lifespan of terminally ill mice bearing tumors.	[85]

5. Potential clinical implications

As a major area of investigation in cancer research, BMI1 expression is often increased in cancer and is linked to tumor progression and invasion, except for endometrial cancer [46]. In nasopharyngeal carcinoma and pancreatic cancer, BMI1 activates the PI3K/Akt signaling pathway to promote tumor relapse [44,45]. Therefore, downregulation of BMI1 has become the goal of many cancer treatments. As mentioned previously, BMI1 inhibitor suppressed tumor growth and promoted cell apoptosis. However, some studies have reported that the expression of BMI1 in specific cell types can promote the heart to resist stress, such as MI, high glucose, aging and oxidative stress. Consequently, we need to consider cardiovascular side effects while applying systemic BMI1 blockers to suppress tumors. A short treatment could be of benefit to anti-tumor, but a prolonged one could become deleterious. Then we also need to consider the cell type-specific roles of BMI1. For example, silencing BMI1 in cardiac fibroblasts attenuated ischemia-induced cardiac fibrosis and heart failure, but ablation of BMI1-expressing progenitor cells impaired the angiogenic response to MI. Furthermore, BMI1 exerts different effects in the cardiac system under different stress stimuli. The roles of BMI1 in cancer and cardiac biology are shown in Table 1. These data raise concerns about therapies that rely on systemic inhibition of BMI1 to combat cancers, and argue for the tumor-targeted application of these anti-cancer molecules. Accordingly, manipulating the expression of BMI1 requires an accurate delivery system, such as Adeno-associated virus (AAV) and Nanocarrier delivery system. Another potential strategy needs to be developed in the further study to manipulate BMI1 expression following cancer treatment in order to prevent future cardiovascular diseases.

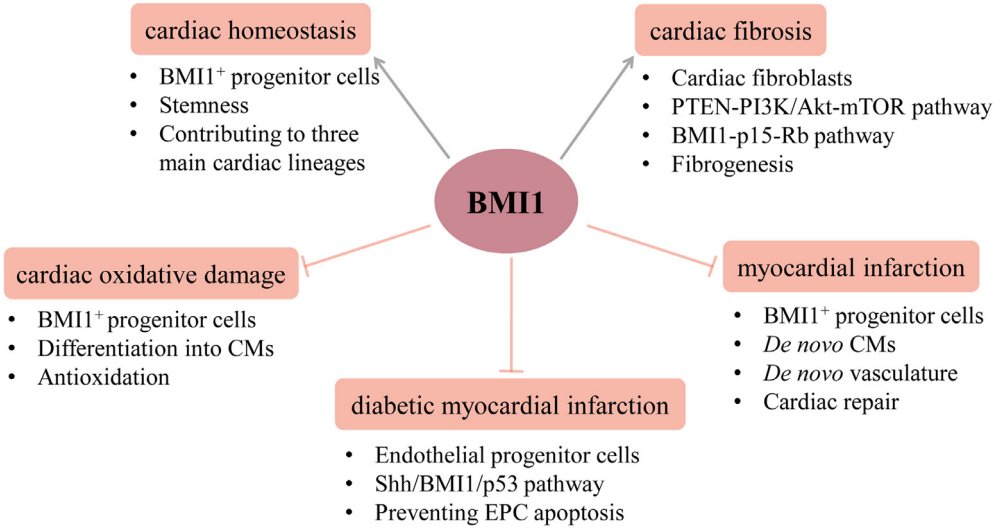

Fig. 2. A summary of BMI1 function in the heart. BMI1, as a significant regulator, participates in the regulation of cardiac homeostasis and some cardiovascular diseases, and the studies to date mainly report the impact of BMI1 in cardiac fibrosis, myocardial infarction and cardiac oxidative damage. Some potential signaling pathways are involved in the progression to heart failure regulated by BMI1, and BMI1$^+$ cardiac cells are the main contributors to cardioprotection in response to myocardial infarction as well as cardiac oxidative stress.

6. Conclusions

BMI1, a well-known oncoprotein, is crucial to the initiation and progression of a variety of malignancies. The emerging studies have elucidated the novel functions of BMI1 beyond tumorigenesis. As a key stem cell regulator, it is well established that BMI1 is highly expressed in cancer stem cells and correlate with tumor growth, tumor metastasis, and chemo-resistance. Similarly, emerging studies have also uncovered that BMI1 is present in cardiac stem/progenitor cells and acts as an important regulatory factor in cardiac pathology. Meanwhile, BMI1 promotes tumorigenesis via signaling transduction, such as BMI1/ PTEN/PI3K/Akt pathway. Surprisingly, some BMI1-involved signaling pathways in tumorigenesis were also play a role in cardiovascular disorders, just as mentioned above. BMI1 as well as $BMI1^+$ cardiac cells respond quickly to various pathological internal/external insults, such as ischemia, cardiac oxidative stress, and cardiac fibrosis (Fig. 2). Additionally, BMI1 plays potential roles in some rapidly developing therapies, such as direct cardiac reprogramming and cell-based therapies, elucidating the possibility that BMI1 could be used as an effective molecular target to compromise cardiac function. Furthermore, the discovery of small molecule inhibitors of BMI1, which were proved effective in cancer treatment by a number of preclinical studies, may extend to the treatment for certain cardiovascular diseases with BMI1 overexpression.

Despite the growing facts about BMI1 in cardiac biology, yet many controversies and unknowns still exist. Although many documented studies have illustrated that BMI1, a significant regulatory factor, mediated CM turnover and contributed to cardiac regeneration in homeostasis as well as in response to heart injuries, the disclosure of the precise regulatory pathways still require multiple parallel fields of study. It is also poorly understood if there are upstream inputs that modulate BMI1 function and molecular mechanisms that underlie the activation of $BMI1^+$ cardiac stem cells in response to pathological stimuli. In addition, it remains unclear whether BMI1 owns potential effects in other frequent cardiac disorders, for instance, ischemia-reperfusion injury, cardiac hypertrophy, and cardiomyopathy. Moreover, although there have been researches that demonstrated the impact of BMI1 on cardiac therapies, how to translate these basic research findings into clinical therapeutic strategies is absolutely the greatest challenge.

From tumorigenesis to cardiovascular diseases, the effects of BMI1 are increasingly understood. With the utilization of more innovative technologies and the implementation of interdisciplinary cooperation in the further investigation into BMI1 function, our understanding of BMI1 in the heart will expand rapidly. And further characterization of the mechanisms underlying cardiac physiology and pathology may provide new opportunities for therapeutic applications.

Outstanding questions

To further investigate the critical roles of BMI1 and apply it into treatment for cardiovascular diseases, there is much to be optimized, including:

1. A precise understanding of the characteristics and subpopulations of these BMI1-positive cells, for example, how these cells interact with cardiomyocytes and nonmyocyes.
2. The crosstalk between BMI1-mediated pathways in cancer and the heart requires further determination.
3. Cardiovascular effects of selective small molecule BMI1 inhibitors which are proved effective in cancer treatment.
4. Studies investigating the application of small molecule BMI1 inhibitors in cardiovascular disorders which are accompanied with high expression of BMI1 are needed.

Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE, PubMed, and references from relevant articles using the search terms “BMI1”, “B lymphoma Mo-MLV insertion region 1”, “B cell-specific Moloney murine leukemia virus integration site 1”, “cardio*” and “heart”. Only articles published in English between 1975 and 2020 were included.

Contributors

Dan Yang, Di Fan and Qi-Zhu Tang contributed to the conception and design of the review. The first draft of the manuscript was written by Dan Yan and Han-Qing Liu; Zheng Yang, Di Fan and Qi-Zhu Tang critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Declaration of Competing Interest

The authors declare that they have no conflicts of interests.

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