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REVIEW ARTICLE

Emerging Roles of Meis1 in Cardiac Regeneration, Stem Cells and Cancer

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Abstract: Meis1 is a member of three-amino-acid loop extension (TALE) homeodomain transcription factors. Studies in the last decade have shown that Meis1 has crucial roles in cardiac regeneration, stem cell function, and tumorigenesis. We have recently demonstrated that knocking out of Meis1 in adult cardiomyocytes resulted in the induction of cardiomyocyte proliferation. This suggests that targeting of Meis1 might be utilized in the manipulation of cardiomyocyte cell cycle post cardiac injuries. In addition, hematopoietic stem cell (HSC) specific deletion of Meis1 leads to *in vivo* expansion of HSCs pool. Thus, targeting Meis1 may lead to not only cell cycle entry but also *ex vivo* and *in vivo* expansion of HSCs. On the other hand, Meis1 transcriptionally regulates the expression of hypoxic tumor markers, namely Hif-1α and Hif-2α. Hif-1α and Hif-2α are involved in the induction of cytoplasmic glycolysis and scavenging of reactive oxygen species (ROS), respectively. This review aims to highlight emerging roles of Meis1 towards development of new therapeutic approaches in the treatment of myocardial injuries, bone failure, and cancer.

Keywords: Meis1, cardiac regeneration, stem cell expansion, cancer metabolism, and cancer stem cells.

1. INTRODUCTION

Meis1, myeloid ecotrophic insertion site 1, was discovered in BXH-2 mouse leukemia model as a common viral integration site [1]. Meis1 is a member of 3-amino-acid loop extension class transcription factors that activate their target genes by associating with Hox transcription factors [2]. Through its binding domains in the N terminus, Meis1 interacts with its cofactors such as the transcription factors Pbx1 and Hoxa9 [3, 4]. Meis2 and Meis3 are the two other proteins that belong to the same family (Fig. **1**). All of the Meis family members were identified by sequence similarity [5]. Meis2 and Meis3 protein sequences demonstrate a high degree of similarity with Meis1 (83% and 66% respectively) [6].

Meis1 function has been studied in various types of tissues. In retinal progenitor cells [7] and olfactory epithelial cells [8] Meis1 was shown to sustain the cells in an undifferentiated state. Meis1 is highly expressed in thymic epithelial cells with immature progenitor phenotype [9]. Meis1 plays a critical role in homeostasis by maintaining the epidermal stem cells in the bulge region of the epidermis. Meis1 is highly expressed in the bulge region of the hair follicle, which is one of the stem cell niches. The number of these adult stem cells decreases by the disruption of Meis1 in the mouse epidermal tissue [10]. Interestingly, epidermal disruption of Meis1 is involved in tumor development and malignant conversion, suggesting a multi-functional model for Meis1 in the epidermis [10]. In addition, Meis1 has been shown to be involved in tumorigenesis of neuroblastomas, nephroblastomas, ovarian carcinomas, prostate cancer, non-small cell lung adenocarcinoma and leukemia [11-16]. Although correlations have been made regarding Meis1 and tumorigenesis, the molecular mechanism behind it remains undetermined.

Meis1 is greatly expressed in primitive hematopoietic populations while its expression decreases throughout differentiation [4, 17]. Meis1$^{-/-}$ mice die around embryonic day 11.5-14.5 by virtue of defects in hematopoiesis and vascularization [18-20]. In the liver of Meis1$^{-/-}$ mice embryos, HSC niches are severely underdeveloped and the number of colony-forming cells is significantly low, highlighting a critical function of Meis1 in HSC regulation [18-20]. We have shown that inducible Meis1 deletion in HSCs leads to the loss of HSC quiescence, followed by robust HSC expansion and exhaustion *in vivo* [21]. Serial transplantation of Meis1 knockout HSCs consequently lead to bone marrow (BM) failure demonstrating requirement of Meis1 in HSC function [3, 21]. Meis1 is also an important regulator of the redox state of HSCs. Deletion of Meis1 results in downregulation of Hif-1α and Hif-2α expression and concomitant elevation of ROS levels and apoptosis in hematopoietic compartment. Manipulation of ROS levels in Meis1 knockout

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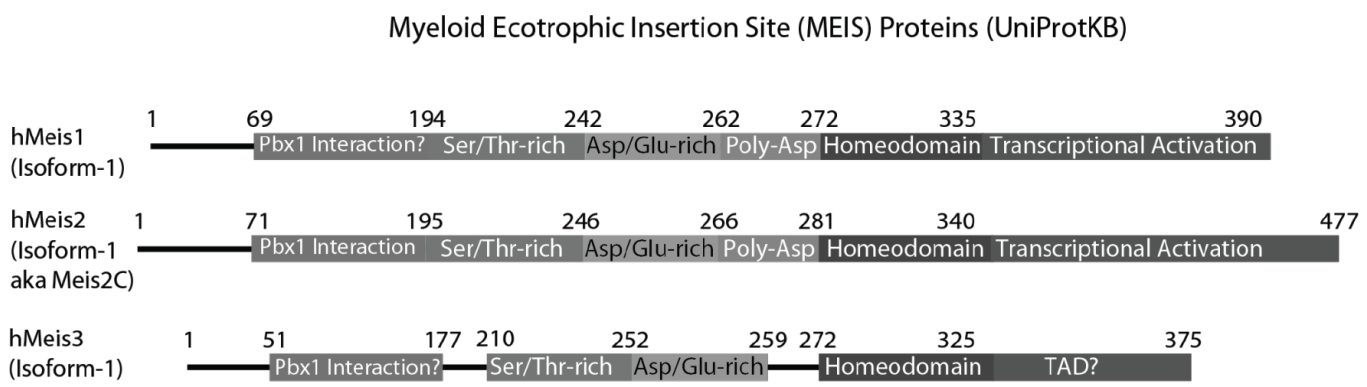

Fig. (1). Domain structure of MEIS proteins: Meis1, Meis2 and Meis3 are members of the TALE homeodomain transcription factors. MEIS proteins contain Pbx1 interaction domains, Ser/Thr and Asp/Glu rich domains. Meis1 and Meis2 (also known as Meis2C) contain Poly-Asp region followed by a highly conserved Homeobox region. MEIS proteins largely differ at their C terminus where transcriptional activation domain (TAD) is located.

HSCs by use of anti-oxidants recovers ROS related bone marrow failure and loss of HSC function [21].

Apart from the role of Meis1 in the regulation of HSC quiescence, it was shown as a transcriptional regulator of neonatal heart regeneration [22]. In mice, Meis1 expression is gradually upregulated from postnatal day 1 (P1) to postnatal day 7 (P7). In contrast to this upregulation, regenerative capacity of the heart is diminished [22]. We have demonstrated that Meis1 regulates cell cycle arrest in cardiomyocytes [22]. Moreover, conditional deletion of Meis1 in the adult heart results in reactivation of cardiomyocyte proliferation [22].

Studies showed that Meis1 is an integral part of the transcriptional network that regulates cardiomyocyte cell cycle, HSC maintenance and cellular metabolism. These findings suggest that Meis1 could be a potential therapeutic target for various conditions including altering the cancer metabolism, targeting cancer stem cells, HSC expansion, and cardiac regeneration.

2. EMERGING ROLE OF MEIS1 IN CARDIAC REGENERATION

Cardiac regeneration comprises one of the most important context of regenerative medicine (reviewed in [23]. Regenerative capacity of heart may vary between and within species [24, 25]. Some organisms with relatively simple anatomical structures such as zebrafish and newt have high capacity of regeneration [24, 25]. These organisms can regenerate myocardium and vasculature after 20% amputation of the ventricular apex. Cardiac regeneration occurs over a two-month period through dedifferentiation of cardiomyoctes marked with sarcomeric disassembly and successve cardiomyocyte [26-28]. Unlike these organisms, the adult mammalian heart cannot regenerate after injury [29-31]. Its response to injury is largely restricted to scar formation following the damage to cardiac tissue [32]. Recent studies, on the other hand, suggest that cardiac stem cells play a key role in the recovery of myocardium after an injury [33, 34]. It was shown that newly regenerated cardiomyocytes are mostly derived from pre-existing cardiomyocytes [26, 35]. Recent studies indicate that adult human heart has residual level of cardiomyocyte turnover and this recovery mechanism may involve stem cells. In addition, rate of cardiomyocyte turnover was shown to decrease proportionally to the age, such that the rate is 1% per year at the age of 20. Moreover, the rate decreases to 0.4% around 75 years of age and 45% of cardiomyocytes can be replaced throughout human life [36-38]. Various approaches are associated with decreasing the rate of cardiomyocyte loss by inhibiting apoptosis, inducing re-entry to cell cycle of cardiomyocytes for enhancing cardiomyocyte proliferation and using cardiomyocytes, bone marrow and skeletal muscle cells for cell therapy [39-42].

Cell cycle is a vital process for all of the cell types and is regulated by a group of complex proteins. Major cell cycle regulators include cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors (CDKIs), CDK activating kinases (CAK) and retinoblastoma (Rb) family proteins. Cyclin/CDK complex plays a major role in cell cycle as a positive regulator and this complex requires activation by CAK *via* phosphorylation [30, 39, 43]. Function of this complex is also controlled by CDKIs including Cip/Kip family ($p21^{Cip1}$, $p27^{Kip1}$, $p57^{Kip2}$) and Ink4 family ($p15^{Ink4b}$, $p16^{Ink4a}$, $p18^{Ink4c}$, $p19^{Ink4d}$). The members of the families bind to Cyclin-D/E/A-dependent kinases and CyclinD-CDK4/6 complex respectively and inhibit their activity.

Majority of the studies show that CDKI levels increase in adult cardiomyocytes and their activity is associated with repression of positive cell cycle regulators such as cyclins and CDKs [44-47]. Several studies demonstrated that Cdk2 and c-myc are the cell cycle regulators that play roles in increasing the expression levels of cyclins and CDKs, such as CDK4, and induction of cardiomyocyte growth respectively [48]. In addition, deletion of CDKI $p27^{Kip1}$ or immunodepletion of $p21^{Cip1}$ in cardiomyocytes leads to progression to S phase, thus induces an increase in cardiomyocyte proliferation and heart size [47, 49]. Recently, Meis1 deletion was shown to induce upregulation of CDKs and downregulation of CDKIs such as p16, p15 and $p19^{ARF}$ and p21 and p57 [22]. Moreover, Meis1 deletion causes upregulation of positive cell cycle regulators such as MCM3, Chek1 and Ccnd2 and downregulation of negative cell cycle regulators such as APbb1, TP53 and Gpr132 [22]. Targeting Meis1 is a plausi-

ble mechanism to induce cardiomyocyte proliferation (Fig. **2**).

Several studies addressed the involvement of Meis1 in the cardiomyopathies. 2p14 microdeletions associated with Meis1 and actr2, and studies suggest that they might be responsible from deafness and cardiomyopathy observed in patients with 2p14 microdeletions [50]. Intriguingly, Meis1 has been associated with restless legs syndrome in a genome-wide association analysis [51]. Thireau *et al.* (2017) showed that RLS patients with Meis1 variants could be determinant for autonomic imbalance and may be potentially at risk for development cardiovascular issues [52].

3. REGULATION OF HEMATOPOIETIC STEM CELL METABOLISM BY MEIS1

HSCs are recognized with their high differentiation and self-renewing capacity, as well as their responsibility of generating blood cells throughout life. Considering the hypoxic environment, HSCs generally reside in endosteal regions of BM that is the zone responsible for vascular organization with partition of capillaries that constitute the arteriols [53-55]. The endosteal niches attest to higher glycolytic flux and their partial pressure of oxygen is very low, which results in limited BM perfusion where the blood attains access into sinusoids through the capillaries [56]. Considering all these properties, especially low oxygen tension, the endosteal region is thought to represent the hypoxic niche of HSCs.

Stem cells generally reside in quiescent state because of their metabolic adaptation to hypoxic niche [57]. Even though importance of hypoxic conditions was known for several stem cells, there was not enough knowledge about metabolic phenotype and its regulatory pathways or how metabolism relates to the cell cycle of stem cells [58, 59]. To this end, we have recently shown that cell cycle of the HSCs can be regulated transcriptionally and metabolically by involvement of Meis1 [21, 60]. We have shown that HSCs prefer anaerobic glycolysis instead of the mitochondrial respiration in order to generate energy with a lower rate of metabolism in a quiescent state (reviewed in and references there in [61]). Thus, their unique glycolytic metabolic phenotype allows tolerance to low oxygen tension and minimize oxidative damage. In addition, murine HSCs and human hematopoietic progenitor and stem cells (HPSCs) are characterized by low mitochondrial potential (MP) [62]. Two major transcriptional regulators, Hif-1α and Meis1, are involved in low MP profile, hypoxic response, and glycolytic metabolism of HSCs [21, 63].

Hif-1 is an essential regulatory transcription factor for cellular and systemic responses in hypoxic conditions. Hif-1, when stabilized, causes a shift from mitochondrial oxidative phosphorylation to glycolysis [64-66]. It is a heterodimeric protein that is composed of two subunits, Hif-1α and Hif-1β. Hif-1α is known as an oxygen regulated subunit that can control the main Hif-1 function and forms a complex with constitutively expressed Hif-1β [63]. Hif-1α has a key role in maintaining quiescence of HSCs and stress resistance [56] as well as in stabilization of protein [64-66] or transcriptional activation [67-70]. Meis1 is a transcription factor that involves in the regulation of HSC metabolism through the optimal expression of Hif-1α [60]. Meis1 and its cofactors Pbx1 and HoxA9 cooperatively take role in Hif-1α activation

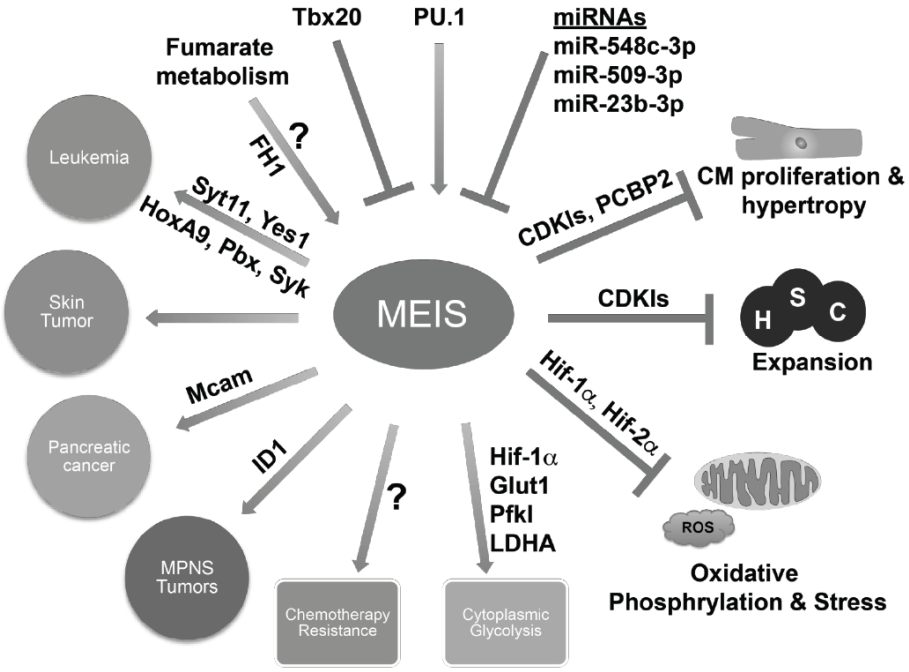

Fig. (2). Molecular pathways and cellular processes related to MEIS: Meis1 has been shown to indirectly, and directly regulated at transcriptional and posttranscriptional levels by FH1, PU.1, Tbx20, and miRNAs. Meis1 knockout studies suggested that cardiomyocytes and HSCs could be expanded. Meis1 also involved in metabolic and oxidative stress through modulation of Hif1a, Hif2a, and Hif1a target genes involved in cytoplasmic glycolysis. A number of studies, perhaps associated with preferential induction of cytoplasmic glycolysis by Meis1, showed the involvement and correlation with cancer progression, invasion, and migration. MPNS: Malignant peripheral nerve sheet, ROS: Reactive oxygen species. CDKIs: Cyclin dependent kinase inhibitors, HSC: Hematopoietic stem cells, CM: Cardiomyocyte.

through conserved Meis1, Pbx1, HoxA9 binding sites in Hif-1α gene [62].

We have recently showed that Meis1 plays a major role in anaerobic glycolysis in the hypoxic niche of HSCs by positively regulating expression of not only Hif-1α but also Hif-2α [21, 63]. Meis1 deletion in HSCs down regulates expression of both Hif-1α and Hif-2α. The role of Hif-1α and Meis1 in anaerobic metabolism was shown by conditional and tissue specific deletion of Hif-1α and Meis1 in HSCs *in vivo*. Takubo and his colleagues (2010) showed that conditional deletion of Hif-1α in BM initiates loss of HSC quiescence, increases HSC cycling and induces loss of long-term repopulation [71]. Our studies demonstrated that the shifting from cytoplasmic glycolysis to mitochondrial oxidative phosphorylation can be triggered by deletion of Hif-1α or Meis1 [21, 63]. As a result, a lower rate of glycolysis and increased mitochondrial activity occur, which leads to an increase in ROS and loss of HSC quiescence.

As discussed above, murine HSCs utilize glycolysis rather than mitochondrial oxidative phosphorylation as their primary energy source but what human hematopoietic stem and progenitor cells (HSPCs) use remained unknown till recently. We recently reported that human HSPCs own similar metabolic characteristics as shown by high levels of glycolysis and low levels of oxygen consumption [62]. In addition, repopulation ability of human low (mitochondrial potential) MP cells or HSPCs is markedly better than high MP cells [62]. Moreover, Hif-1α expression is markedly high in human HSPCs. Similar to murine counterparts, Meis1 has a key role in the regulation of human HSPCs through regulation of Hif-1α together with its cofactors Pbx1 and Hoxa9 [62].

The role of Meis1 is not only limited to the regulation of HSC metabolism, but it is also responsible for the regulation of oxidative stress through transcriptional regulation of Hif-2α [21, 63]. Hif-1α and Hif-2α generally have discrete targets even though they are extremely homologous and may also target similar genes such as Glut1 and VEGF. A well-defined example of having different targets is that while the glycolytic enzymes such PGK, LDHA are exclusively stimulated by Hif-1α, expression of antioxidant enzymes such as catalase, superoxide dismutase and glutathione peroxide are regulated by Hif-2α [72, 73]. Increased ROS, multiorgan dysfunction, cardiac hypertrophy, hepatic steatosis, defects in spermatogenesis and hematopoiesis are the main challenges that Hif-2α knockout mice face [72, 74]. During mitochondrial oxidative phosphorylation, generation of ROS occurs. High levels of ROS cause senescence or apoptosis in HSCs. Thus, increase in ROS generation in Meis1 knockout HSCs associated with down-regulation of Hif-2α in HSC (Fig. **2**) [21]. Moreover, N-acetyl-L-cysteine (NAC) treatment, a ROS scavenger, was efficiently been used to compensate oxidative damage in Meis1 knockout HSCs [21].

4. INVOLVEMENT OF MEIS1 IN CARCINOGENESIS, CANCER STEM CELL ESTABLISHMENT AND METABOLISM

Cell cycle regulation is one of the most significant areas of research with implications on regenerative biology and treatment of cancer [75-77]. Dysregulation of cell cycle checkpoints results in genomic and chromosomal instability that contribute to carcinogenesis [78, 79]. Cancer cells metabolize glucose at an elevated level by cytoplasmic glycolysis compared to normal cells even oxygen is available, which is known as Warburg effect [80]. This allows survival of cancer cells in hypoxic microenvironments of tumor [81]. Even though there is a relationship between metabolic adaptation and up-regulation of Meis1 in various malignant cells, functions of Meis1 and its cofactors remain to be discovered in the process of carcinogenesis, cancer stem cell establishment and involvement in cancer metabolism.

4.1. Regulation of Meis1 Expression

A number study demonstrated that Meis1 expression is modulated by transcription factors, miRNAs and indirect metabolic changes. Xiang FL *et al.* (2016) demonstrated that Tbx20 overexpression leads to adult cardioymcyte proliferation associated with downregulation of Meis1 and p21, two important regulators of postnatal cardiomyocyte cell cycle arrest [82, 83]. In addition, they have shown that Meis1 was directly bound and repressed by Tbx20 in cardiomyocytes. Pandey *et al.* (2016) shown that miRNAs miR-548c-3p, miR-509-3p, and miR-23b-3p have been found to downregulate expression in cardiomyocytes and trigger adult cardiomyocyte proliferation [84]. This was evident with induction of EdU+, Ph3+ cardiomyocytes and upregulation CDK2 expression post treatment with miRNAs targeting Meis1. It was shown that the loss of fumarate hydratase (Fh1), which is involved in TCA cycle and fumarate metabolism, in leukemia stem cells leads activation of Meis1/Hoxa9 oncogenic pathway [85]. These suggested that metabolic changes could trigger Meis1 pathway activation during leukemia development. Intrıguingly, it was found that Dnmt3a mutations could lead to reactivation of oncogenic Meis1 pathway in acute myeloid leukemia even at the absence of fusion [86]. A recent study by Zhou *et al.* (2015) demonstrated that PU.1 involved in leukemiogenesis and maintenance of proliferation through transactivation of Meis1 expression in non-MLL U937 cells [87].

Involvement of Meis1 in cancer was firstly shown by a study in myeloid leukemia cells of acute myeloid leukemia (AML) patients [14, 88-90]. Increased expression of Meis1 was detected in BM of acute lymphoid leukemia (ALL) and AML patients (Table **1**) [18, 91]. Overexpression of Meis1 accelerates the onset of the disease in murine AML models [92, 93]. Meis1 associates with Hox proteins in leukemic transformation [14, 17]. Hoxa9 along with Meis1 remarkably accelerate leukemogenesis [14]. In addition, Meis1 is upregulated in neuroblastomas [11-13], nephroblastomas [15], ovarian carcinomas [16], which suggest potential involvement of Meis1 in cancer development. Furthermore, a recent study on epidermis has shown that Meis1 is involved in the development of papilloma and formation of skin tumors [10].

4.2. Meis1 Associated Carcinogenesis

Many studies suggested the involvement of Meis1 driven leukemia. Meis1 along with Hoxa9 and Pbx3 often found to be driving hematopoietic transformation in MLL-rearranged leukemia [94]. Meis1, especially associated with leukemia

Table 1. Differential expression of Meis1 gene and its cofactors in various cancer types.

Cancer Type	Observations	Reference
Leukemia (various)	Upregulation of Meis1 and HoxA9	[89-91, 113-115]
Chronic lymphocytic leukemia	Down regulation Meis1	[103]
MLL-rearranged leukemia	Upregulation of Meis1, Pbx3 and HoxA9	[94]
Neuroblastoma	Upregulation of Meis1	[116]
Nephroblastoma	Upregulation of Meis1	[117]
Ovarian carcinoma	Upregulation of Meis1 and Pbx	[118]
Skin tumor	Upregulation of Meis1	[10]
Clear cell renal cell carcinoma	Forced overexpression of Meis1	[119]
Esophageal Squamous Cell Carcinoma	Down regulation Meis1	[106]
Acute myeloid leukemia	Upregulation of Meis1	[95]
AML1-ETO-positive acute myeloid leukemia	Upregulation of Meis2	[97]
Pancreatic cancer	Activation of Mcam by Meis1	[98]
Malignant peripheral nerve sheath tumors	Upregulation of Meis1	[99]

stem cell maintenance while Pbx3 involved in leukemia cell survival. Similarly in acute myeloid leukemia, Meis1 found to be overexpressed in majority of patients (67 %) [95]. Importantly, a high level of Meis1 expression was found to be associated with resistance to conventional chemotherapies. Higher expression of Meis1 and Hoxa9 also found in various types of childhood acute leukemias [96]. Intriguingly, Meis2, which share identical homeobox domain with Meis1, has been shown to overexpressed and acting as oncogenic partner in AML1-ETO-positive acute myeloid leukemia through induction of Yes1 proto-oncogene expression [97].

Meis1 has been found to activate metastatic cell adhesion molecule (Mcam) expression so that it involves in induction of pancreatic cancer cell migration [98]. Patel *et al.* (2016) performed an shRNA screen and demonstrated that Meis1 involves in progression of malignant peripheral nerve sheath tumors through activation of ID1, thereby increasing survival [99]. Study by Yokoyama *et al.* (2016) further demonstrated that Meis1 promotes leukemia development through transactivation of Sytl1 expression and CXCL12/CXCR4 signaling [100]. Meis1 was also shown to involve in regulation of oxidative stress by transactivating hepatic leukemia factor in leukemia [101]. Study by Zhang *et al.* (2016) demonstrated that Meis1 transactivates PCBP2, which is known to negatively modulate cardiac hypertrophy, and inhibits angiotensin II-induced cardiomyocyte hypertrophy [102].

4.3. Differential Expression of Meis1

Rani L *et al.*, (2017) showed that expression of Meis1 in chronic lymphocytic leukemia (CLL) were significantly downregulated compared to B-cells from control group [103]. In addition, the CpG islands in the promoter region of Meis1 found to be hypermethylated. Meis1 along with TCF7L1 and TCF4 genes found to be differentially expressed in gastric carcinogenesis [104, 105]. Analysis of Meis1 and MAML1 in esophageal squamous cell carcinoma samples showed that 9 out of 51 samples with downregulation of Meis1 where Meis1 is negatively correlated with MAML1 expression [106]. A recent study based on phosphor-proteomic analysis by Mohr *et al.* (2017) showed Meis1 induced Syk protein expression and activity in acute myeloid leukemia [107]. Besides, Cui *et al.* (2014) demonstrated that Meis1 overexpression negatively modulate androgen receptor activity and expression in prostate cancer. In addition, Meis1 inhibited LNCaP cell growth suggesting Meis1 as repressor of androgen receptor [108]. Similarly, Meis1 overexpression inhibited non-small-cell lung cancer cell proliferation. On the contrary, downregulation of Meis1 was associated with increased DNA synthesis and proliferation.

Wong and colleagues (2007) showed that Meis1 is involved in cancer stem cell function as shown in leukemia stem cell (LSC) establishment, LSC frequency through regulating cancer stem cell self-renewal, induction of differentiation arrest, and establishment of *in vivo* LSC generation from hematopoietic progenitors [109]. Intriguingly, Meis1 expression is reduced in prostate cancer, which suggests the involvement of Meis1 in prostate cancer development [110]. The reason why Meis1 is differentially expressed in different types of tumors is not known yet. However, it suggests that Meis1 is involved with tumorigenesis of different types of tumors through different mechanisms. Moreover, Meis1 represses non-small-cell-lung adenocarcinoma cancer cell proliferation [111]. This situation is similar with results of our study on hematopoietic stem cells, in which expression of Meis1 promotes HSCs to stay in quiescence state [21] and overexpression of Meis1 also reduces neonatal and adult cardiomyocyte proliferation [22]. All these findings suggest

that Meis1 has distinct functions in the proliferation of a cell. This could be dependent on the presence of cofactors and depending on the type of metabolism cell needed. For instance, we believe glycolytic cancer cell metabolism might be triggered by increased expression of Meis1 in cancer, which in turn upregulates cytoplasmic glycolysis through Hif-1α and down regulates oxidative damage through Hif-2α.

Environmental and intrinsic stem cell factors influence stem cell fate, function and metabolism [112]. Meis1 and Hif-1α are two regulators that play critical role in HSC metabolism and function [21, 56]. In addition, Meis1 controls oxidative stress response through Hif-2α regulation. Increased expression of Meis1 and its cofactors are observed in HSCs and a wide variety of leukemia [1, 4, 14, 18, 89-91, 93] and in other cancer cell types [11-13, 15, 16]. Even though it is known that Meis1 plays a role in cancer and HSCs, further studies are required to understand its role in the mechanism of transformation and regulation of cancer cell metabolism and cancer stem cell function.

5. TARGETING MEIS1 IN HEMATOPOIETIC STEM CELL TECHNOLOGIES

HSCs underlie BM transplantation and demonstrate great importance in targeted gene therapies. Transplantation of HSCs are applied in the treatments of leukemia, lymphoma and in the autoimmune disorders [120]. An HLA-matched donor is required to overcome immunologic responses by the host. In addition, accessibility to enough quantity of HSCs from donor is necessary for successful engraftment [121]. Therefore, it is required to develop *ex vivo* methods to provide efficient number of HSCs. *Ex vivo* HSC expansion approaches mainly rely on growth factors and cytokines [120]. The balance between proliferation and quiescence of HSCs is strictly controlled to ensure homeostasis and maintenance of HSCs lifelong [122]. However, small molecules that target quiescence factors involved in HSC quiescence have not been widely used for expansion of HSCs. It is anticipated that hematopoietic small molecules will bring new approaches to the expansion of HSCs in cell-culture.

Ex vivo expansion of HSCs may harbor many difficulties, such as decreased self-renewal ability, senescence, apoptosis, and differentiation. Apart from this, knowledge about constituents of HSC microenvironment and regulators of HSC function in *ex vivo* expansion procedure is restricted. Many studies concentrated on cytokines and growth factors when defining how to expand HSCs in *ex vivo* culture. Cytokines including thrombopoietin (TPO), FL3, IL3, IL6, IL11 and stem cell factor (SCF) have been proved to have function in HSC expansion [120]. Cytokines stimulate HSCs that are arrested in G_0 phase to enter the cell cycle by up-regulating factors responsible in self-renewal and by down-regulating inhibitors of cell cycle. Interestingly, p38 and some other factors that inhibit cell cycle are upregulated during *ex vivo* expansion procedure [123-125]. Use of p38 inhibitor was shown to increase *ex vivo* expansion of mouse HSCs [123-125].

Earlier studies showed the applicability of *ex vivo* HSC expansion using small molecules [21, 126, 127]. These studies demonstrated the expansion of human and mouse HSCs utilizing Garcinol (non-specific HAT inhibitor), StemRegenin (AhR antagonist) and Nicotinamide (SIRT1 inhibitor) [122, 127-130]. These studies focused on targeting of cell cycle inhibitors, HSC quiescence regulators and inhibitory factors of *ex vivo* HSC expansion by applying hematopoietic small molecules (HSMs), which induce hematopoiesis or hematopoietic stem cell expansion [128, 131-134]. One of the recently discovered targets for *ex vivo* expansion of HSCs is Meis1 (Fig. **2**). We have previously reported that HSCs could be expanded *in vivo* by specific deletion of Meis1 or Hif-1α genes (Table **2**). This expansion of HSCs was evident in increase in HSC frequency, reduction of the number of HSCs in quiescent state (G_0 phase of cell cycle), and induction of percentage of HSCs in G_1 and S-G_2-M phase of cell cycle [21].

In our previous study, we demonstrated that Meis1 expression is detected in postnatal heart associated with postnatal cardiomyocyte cell cycle arrest. On the other hand, deletion of Meis1 in adult cardiomyocytes was related with induction of cell cycle re-entry [22]. This is similar with the findings from HSC cell cycle that lacks Meis1 in LT-HSCs results in loss of quiescence and increased HSC expansion [21]. These studies clearly showed that Meis1 is likely to have a critical role in cardiomyocyte proliferation as well as HSC pool expansion. Moreover, Meis1 involved in the regulation of cellular metabolism through transcriptional regula-

Table 2. ***In vivo*** **expansion of HSC pool and increased cell cycle activity in Meis1 and Hif-1α knockout HSCs: HSC specific deletion of Meis1 or Hif-1α results in 4.5 and 1.75 fold increase in their HSC pools *in vivo*, respectively. This is accompanied by increased cell cycle activity as measured by increased percentage of cells in G_1 (18%) and S-G_2-M (3%) phase in Meis1$^{-/-}$ HSCs, and increased percentage of cells in G_1 phase (20%) in Hif-1α $^{-/-}$ HSCs. Meis1$^{-/-}$ and Hif-1α $^{-/-}$ long-term hematopoietic stem cell (LT-HSCs) phenotype indicate an altered quiescence in HSCs as well as a tendency to proliferate as we shown previously [21]. * p < 0.05 and ** p < 0.01 compared to WT.**

Genotype	LT- HSC%	Percentage of Cells in Cell Cycle		
		G_0 Phase	G_1 Phase	S-G_2-M Phase
WT	0.0020	82.9±0.2	11.4±0.2	2.0±0.1
Meis1 -/-	0.0092 **	71.2±1.1 **	18.4±1.0 *	3.2±0.4 *
Hif-1α -/-	0.0035 *	77.5±0.8 *	20.9±0.7 **	0.9±0.1

tion of Hif-1α and Hif-2α. Meis1 therapeutics could potentially be useful in various fields of research and treatment of disorders.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

INFORMED CONSENT

This article does not contain any studies with human participants or animals performed by any of the authors.

REFERENCES

[1] Moskow JJ, Bullrich F, Huebner K, Daar IO, Buchberg AM. Meis1, a PBX1-related homeobox gene involved in myeloid leukemia in BXH-2 mice. Mol Cell Biol 1995; 15(10): 5434-43.

[2] Cesselli D, Jakoniuk I, Barlucchi L, *et al.* Oxidative stress-mediated cardiac cell death is a major determinant of ventricular dysfunction and failure in dog dilated cardiomyopathy. Circ Res 2001; 89(3): 279-86.

[3] Ariki R, Morikawa S, Mabuchi Y, *et al.* Homeodomain transcription factor Meis1 is a critical regulator of adult bone marrow hematopoiesis. PLoS One 2014; 9(2): e87646.

[4] Argiropoulos B, Humphries RK. Hox genes in hematopoiesis and leukemogenesis. Oncogene 2007; 26(47): 6766-76.

[5] Hyman-Walsh C, Bjerke GA, Wotton D. An autoinhibitory effect of the homothorax domain of Meis2. FEBS J 2010; 277(12): 2584-97.

[6] von Burstin J, Reichert M, Wescott MP, Rustgi AK. The pancreatic and duodenal homeobox protein PDX-1 regulates the ductal specific keratin 19 through the degradation of MEIS1 and DNA binding. PLoS One 2010; 5(8): e12311.

[7] Heine P, Dohle E, Bumsted-O'Brien K, Engelkamp D, Schulte D. Evidence for an evolutionary conserved role of homothorax/Meis1/2 during vertebrate retina development. Development 2008; 135(5): 805-11.

[8] Tucker ES, Lehtinen MK, Maynard T, *et al.* Proliferative and transcriptional identity of distinct classes of neural precursors in the mammalian olfactory epithelium. Development 2010; 137(15): 2471-81.

[9] Hirayama T, Asano Y, Iida H, Watanabe T, Nakamura T, Goitsuka R. Meis1 is required for the maintenance of postnatal thymic epithelial cells. PLoS One 2014; 9(3): e89885.

[10] Okumura K, Saito M, Isogai E, *et al.* Meis1 regulates epidermal stem cells and is required for skin tumorigenesis. PLoS One 2014; 9(7): e102111.

[11] Geerts D, Schilderink N, Jorritsma G, Versteeg R. The role of the MEIS homeobox genes in neuroblastoma. Cancer Lett 2003; 197(1-2): 87-92.

[12] Jones TA, Flomen RH, Senger G, Nizetic D, Sheer D. The homeobox gene MEIS1 is amplified in IMR-32 and highly expressed in other neuroblastoma cell lines. Eur J Cancer 2000; 36(18): 2368-74.

[13] Spieker N, van Sluis P, Beitsma M, *et al.* The MEIS1 oncogene is highly expressed in neuroblastoma and amplified in cell line IMR32. Genomics 2001; 71(2): 214-21.

[14] Kroon E, Krosl J, Thorsteinsdottir U, Baban S, Buchberg AM, Sauvageau G. Hoxa9 transforms primary bone marrow cells through specific collaboration with Meis1a but not Pbx1b. EMBO J 1998; 17(13): 3714-25.

[15] Dekel B, Metsuyanim S, Schmidt-Ott KM, *et al.* Multiple imprinted and stemness genes provide a link between normal and tumor progenitor cells of the developing human kidney. Cancer Res 2006; 66(12): 6040-9.

[16] Crijns AP, de Graeff P, Geerts D, *et al.* MEIS and PBX homeobox proteins in ovarian cancer. Eur J Cancer 2007; 43(17): 2495-505.

[17] Argiropoulos B, Yung E, Humphries RK. Unraveling the crucial roles of Meis1 in leukemogenesis and normal hematopoiesis. Genes Dev 2007; 21(22): 2845-9.

[18] Imamura T, Morimoto A, Takanashi M, *et al.* Frequent coexpression of HoxA9 and Meis1 genes in infant acute lymphoblastic leukaemia with MLL rearrangement. Br J Haematol 2002; 119(1): 119-21.

[19] Azcoitia V, Aracil M, Martinez AC, Torres M. The homeodomain protein Meis1 is essential for definitive hematopoiesis and vascular patterning in the mouse embryo. Dev Biol 2005; 280(2): 307-20.

[20] Hisa T, Spence SE, Rachel RA, *et al.* Hematopoietic, angiogenic and eye defects in Meis1 mutant animals. EMBO J 2004; 23(2): 450-9.

[21] Kocabas F, Zheng J, Thet S, *et al.* Meis1 regulates the metabolic phenotype and oxidant defense of hematopoietic stem cells. Blood 2012; 120(25): 4963-72.

[22] Mahmoud AI, Kocabas F, Muralidhar SA, *et al.* Meis1 regulates postnatal cardiomyocyte cell cycle arrest. Nature 2013; 497(7448): 249-53.

[23] Aslan GS, Kocabas F. Underlying mechanisms and prospects of heart regeneration. Turkish Journal of Biology,. 2015; Advance online publication, Doi: 10.3906/biy-1506-14.

[24] Oberpriller JO, Oberpriller JC. Response of the adult newt ventricle to injury. J Exp Zool 1974; 187(2): 249-53.

[25] Poss KD, Wilson LG, Keating MT. Heart regeneration in zebrafish. Science 2002; 298(5601): 2188-90.

[26] Jopling C, Sleep E, Raya M, Marti M, Raya A, Izpisua Belmonte JC. Zebrafish heart regeneration occurs by cardiomyocyte dedifferentiation and proliferation. Nature 2010; 464(7288): 606-9.

[27] Kikuchi K, Holdway JE, Werdich AA, *et al.* Primary contribution to zebrafish heart regeneration by gata4(+) cardiomyocytes. Nature 2010; 464(7288): 601-5.

[28] Tate JM, Oberpriller JO. Primary cell culture and morphological characterization of ventricular myocytes from the adult newt, Notophthalmus viridescens. Anat Rec 1989; 224(1): 29-42.
[29] Ahuja P, Sdek P, MacLellan WR. Cardiac myocyte cell cycle control in development, disease, and regeneration. Physiol Rev 2007; 87(2): 521-44.
[30] Pasumarthi KB, Field LJ. Cardiomyocyte cell cycle regulation. Circ Res 2002; 90(10): 1044-54.
[31] Laflamme MA, Murry CE. Heart regeneration. Nature 2011; 473: 326-35.
[32] Porrello ER, Mahmoud AI, Simpson E, *et al.* Transient regenerative potential of the neonatal mouse heart. Science 2011; 331: 1078-80.
[33] Hsieh PC, Segers VF, Davis ME, *et al.* Evidence from a genetic fate-mapping study that stem cells refresh adult mammalian cardiomyocytes after injury. Nat Med 2007; 13(8): 970-4.
[34] Bersell K, Arab S, Haring B, Kuhn B. Neuregulin1/ErbB4 signaling induces cardiomyocyte proliferation and repair of heart injury. Cell 2009; 138(2): 257-70.
[35] Kikuchi K, Holdway JE, Werdich AA, *et al.* Primary contribution to zebrafish heart regeneration by gata4(+) cardiomyocytes. Nature 2010; 464: 601-5.
[36] Porrello ER, Olson EN. Building a new heart from old parts: stem cell turnover in the aging heart. Circ Res 2010; 107(11): 1292-4.
[37] Soonpaa MH, Field LJ. Assessment of cardiomyocyte DNA synthesis in normal and injured adult mouse hearts. Am J Physiol 1997; 272(1 Pt 2): H220-6.
[38] Bergmann O, Bhardwaj RD, Bernard S, *et al.* Evidence for cardiomyocyte renewal in humans. Science 2009; 324(5923): 98-102.
[39] Dowell JD, Field LJ, Pasumarthi KB. Cell cycle regulation to repair the infarcted myocardium. Heart Fail Rev 2003; 8(3): 293-303.
[40] Kirshenbaum LA, de Moissac D. The bcl-2 gene product prevents programmed cell death of ventricular myocytes. Circulation 1997; 96(5): 1580-5.
[41] Murry CE, Wiseman RW, Schwartz SM, Hauschka SD. Skeletal myoblast transplantation for repair of myocardial necrosis. J Clin Invest 1996; 98(11): 2512-23.
[42] Yeh ET, Zhang S, Wu HD, Korbling M, Willerson JT, Estrov Z. Transdifferentiation of human peripheral blood CD34+-enriched cell population into cardiomyocytes, endothelial cells, and smooth muscle cells *in vivo*. Circulation 2003; 108(17): 2070-3.
[43] Obaya AJ, Sedivy JM. Regulation of cyclin-Cdk activity in mammalian cells. Cell Mol Life Sci 2002; 59(1): 126-42.
[44] Brooks G, Poolman RA, McGill CJ, Li JM. Expression and activities of cyclins and cyclin-dependent kinases in developing rat ventricular myocytes. J Mol Cell Cardiol 1997; 29(8): 2261-71.
[45] Brooks G, Poolman RA, Li JM. Arresting developments in the cardiac myocyte cell cycle: role of cyclin-dependent kinase inhibitors. Cardiovasc Res 1998; 39(2): 301-11.
[46] Poolman RA, Brooks G. Expressions and activities of cell cycle regulatory molecules during the transition from myocyte hyperplasia to hypertrophy. J Mol Cell Cardiol 1998; 30(10): 2121-35.
[47] Poolman RA, Gilchrist R, Brooks G. Cell cycle profiles and expressions of p21CIP1 AND P27KIP1 during myocyte development. Int J Cardiol 1998; 67(2): 133-42.
[48] Perez-Roger I, Kim SH, Griffiths B, Sewing A, Land H. Cyclins D1 and D2 mediate myc-induced proliferation *via* sequestration of p27(Kip1) and p21(Cip1). EMBO J 1999; 18(19): 5310-20.
[49] Poolman RA, Li JM, Durand B, Brooks G. Altered expression of cell cycle proteins and prolonged duration of cardiac myocyte hyperplasia in p27KIP1 knockout mice. Circ Res 1999; 85(2): 117-27.
[50] Mathieu ML, Demily C, Chantot-Bastaraud S, *et al.* Clinical and molecular cytogenetic characterization of four unrelated patients carrying 2p14 microdeletions. Am J Med Genet A 2017.
[51] Hammerschlag AR, Stringer S, de Leeuw CA, *et al.* Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. Nat Genet 2017.
[52] Thireau J, Farah C, Molinari N, *et al.* MEIS1 variant as a determinant of autonomic imbalance in Restless Legs Syndrome. Sci Rep 2017; 7: 46620.
[53] Arai F, Hirao A, Ohmura M, *et al.* Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. Cell 2004; 118(2): 149-61.
[54] Calvi LM, Adams GB, Weibrecht KW, *et al.* Osteoblastic cells regulate the haematopoietic stem cell niche. Nature 2003; 425(6960): 841-6.
[55] Zhang J, Niu C, Ye L, *et al.* Identification of the haematopoietic stem cell niche and control of the niche size. Nature 2003; 425(6960): 836-41.
[56] Suda T, Takubo K, Semenza GL. Metabolic regulation of hematopoietic stem cells in the hypoxic niche. Cell Stem Cell 2011; 9(4): 298-310.
[57] Mohyeldin A, Garzon-Muvdi T, Quinones-Hinojosa A. Oxygen in stem cell biology: a critical component of the stem cell niche. Cell Stem Cell 2010; 7(2): 150-61.
[58] Aguilar V, Fajas L. Cycling through metabolism. EMBO Mol Med 2010; 2(9): 338-48.
[59] Buchakjian MR, Kornbluth S. The engine driving the ship: metabolic steering of cell proliferation and death. Nat Rev Mol Cell Biol 2010; 11(10): 715-27.
[60] Simsek T, Kocabas F, Zheng J, *et al.* The distinct metabolic profile of hematopoietic stem cells reflects their location in a hypoxic niche. Cell Stem Cell 2010; 7(3): 380-90.
[61] Uckac PU, Taskaya DG, Kocabas F. Hypoxic Niche of Glycolytic Stem and Progenitor Cells. Arch Stem Cell Res 2014; 1: 1002.
[62] Kocabas F, Xie L, Xie J, *et al.* Hypoxic metabolism in human hematopoietic stem cells. Cell Biosci 2015; 5: 39.
[63] Zhang CC, Sadek HA. Hypoxia and metabolic properties of hematopoietic stem cells. Antioxid Redox Signal 2014; 20(12): 1891-901.
[64] Semenza GL. Hypoxia-inducible factor 1 (HIF-1) pathway. Sci STKE 2007; 2007(407): cm8.
[65] Semenza GL. Regulation of cancer cell metabolism by hypoxia-inducible factor 1. Semin Cancer Biol 2009; 19(1): 12-6.
[66] Semenza GL. Oxygen homeostasis. Wiley Interdiscip Rev Syst Biol Med 2010; 2(3): 336-61.
[67] Gorlach A, Bonello S. The cross-talk between NF-kappaB and HIF-1: further evidence for a significant liaison. Biochem J 2008; 412(3): e17-9.
[68] Hirota K, Fukuda R, Takabuchi S, *et al.* Induction of hypoxia-inducible factor 1 activity by muscarinic acetylcholine receptor signaling. J Biol Chem 2004; 279(40): 41521-8.
[69] Laughner E, Taghavi P, Chiles K, Mahon PC, Semenza GL. HER2 (neu) signaling increases the rate of hypoxia-inducible factor 1alpha (HIF-1alpha) synthesis: novel mechanism for HIF-1-mediated vascular endothelial growth factor expression. Mol Cell Biol 2001; 21(12): 3995-4004.
[70] Rius J, Guma M, Schachtrup C, *et al.* NF-kappaB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1alpha. Nature 2008; 453(7196): 807-11.
[71] Takubo K, Goda N, Yamada W, *et al.* Regulation of the HIF-1alpha level is essential for hematopoietic stem cells. Cell Stem Cell 2010; 7(3): 391-402.
[72] Patel SA, Simon MC. Biology of hypoxia-inducible factor-2alpha in development and disease. Cell Death Differ 2008; 15(4): 628-34.
[73] Scortegagna M, Ding K, Oktay Y, *et al.* Multiple organ pathology, metabolic abnormalities and impaired homeostasis of reactive oxygen species in Epas1-/- mice. Nat Genet 2003; 35(4): 331-40.
[74] Scortegagna M, Morris MA, Oktay Y, Bennett M, Garcia JA. The HIF family member EPAS1/HIF-2alpha is required for normal hematopoiesis in mice. Blood 2003; 102(5): 1634-40.
[75] Funk JO. Cancer cell cycle control. Anticancer Res 1999; 19(6A): 4772-80.
[76] He S, Nakada D, Morrison SJ. Mechanisms of stem cell self-renewal. Annu Rev Cell Dev Biol 2009; 25(1): 377-406.
[77] Park MT, Lee SJ. Cell cycle and cancer. Cell cycle and cancer 2003.
[78] Malumbres M, Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm. Nat Rev Cancer 2009; 9(3): 153-66.
[79] Zhou S, Huang C, Wei Y. The metabolic switch and its regulation in cancer cells. Sci China Life Sci 2010; 53(8): 942-58.
[80] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science 2009; 324(5930): 1029-33.
[81] Denko NC. Hypoxia, HIF1 and glucose metabolism in the solid tumour. Nat Rev Cancer 2008; 8(9): 705-13.
[82] Xiang FL, Guo M, Yutzey KE. Overexpression of Tbx20 in Adult Cardiomyocytes Promotes Proliferation and Improves Cardiac

Function After Myocardial Infarction. Circulation 2016; 133(11): 1081-92.

[83] Ponnusamy M, Li PF, Wang K. Understanding cardiomyocyte proliferation: an insight into cell cycle activity. Cell Mol Life Sci 2017; 74(6): 1019-34.

[84] Pandey R, Yang Y, Jackson L, Ahmed RP. MicroRNAs regulating meis1 expression and inducing cardiomyocyte proliferation. Cardiovasc Regen Med 2016; 3.

[85] Guitart AV, Panagopoulou TI, Villacreces A, *et al.* Fumarate hydratase is a critical metabolic regulator of hematopoietic stem cell functions. J Exp Med 2017; 214(3): 719-35.

[86] Ferreira HJ, Heyn H, Vizoso M, *et al.* DNMT3A mutations mediate the epigenetic reactivation of the leukemogenic factor MEIS1 in acute myeloid leukemia. Oncogene 2016; 35(23): 3079-82.

[87] Zhou J, Zhang X, Wang Y, Guan Y. PU.1 affects proliferation of the human acute myeloid leukemia U937 cell line by directly regulating MEIS1. Oncol Lett 2015; 10(3): 1912-8.

[88] Kawagoe H, Humphries RK, Blair A, Sutherland HJ, Hogge DE. Expression of HOX genes, HOX cofactors, and MLL in phenotypically and functionally defined subpopulations of leukemic and normal human hematopoietic cells. Leukemia 1999; 13(5): 687-98.

[89] Thorsteinsdottir U, Kroon E, Jerome L, Blasi F, Sauvageau G. Defining roles for HOX and MEIS1 genes in induction of acute myeloid leukemia. Mol Cell Biol 2001; 21(1): 224-34.

[90] Wong P, Iwasaki M, Somervaille TC, So CW, Cleary ML. Meis1 is an essential and rate-limiting regulator of MLL leukemia stem cell potential. Genes Dev 2007; 21(21): 2762-74.

[91] Rozovskaia T, Feinstein E, Mor O, *et al.* Upregulation of Meis1 and HoxA9 in acute lymphocytic leukemias with the t(4 : 11) abnormality. Oncogene 2001; 20(7): 874-8.

[92] Fischbach NA, Rozenfeld S, Shen W, *et al.* HOXB6 overexpression in murine bone marrow immortalizes a myelomonocytic precursor *in vitro* and causes hematopoietic stem cell expansion and acute myeloid leukemia *in vivo*. Blood 2005; 105(4): 1456-66.

[93] Pineault N, Abramovich C, Ohta H, Humphries RK. Differential and common leukemogenic potentials of multiple NUP98-Hox fusion proteins alone or with Meis1. Mol Cell Biol 2004; 24(5): 1907-17.

[94] Guo H, Chu Y, Wang L, *et al.* PBX3 is essential for leukemia stem cell maintenance in MLL-rearranged leukemia. Int J Cancer 2017; 141(2): 324-35.

[95] Liu J, Qin YZ, Yang S, *et al.* Meis1 is critical to the maintenance of human acute myeloid leukemia cells independent of MLL rearrangements. Ann Hematol 2017; 96(4): 567-74.

[96] Adamaki M, Lambrou GI, Athanasiadou A, Vlahopoulos S, Papavassiliou AG, Moschovi M. HOXA9 and MEIS1 gene overexpression in the diagnosis of childhood acute leukemias: Significant correlation with relapse and overall survival. Leuk Res 2015; 39(8): 874-82.

[97] Vegi NM, Klappacher J, Oswald F, *et al.* MEIS2 Is an Oncogenic Partner in AML1-ETO-Positive AML. Cell Rep 2016; 16(2): 498-507.

[98] von Burstin J, Bachhuber F, Paul M, Schmid RM, Rustgi AK. The TALE homeodomain transcription factor MEIS1 activates the prometastatic melanoma cell adhesion molecule Mcam to promote migration of pancreatic cancer cells. Mol Carcinog 2017; 56(3): 936-44.

[99] Patel AV, Chaney KE, Choi K, Largaespada DA, Kumar AR, Ratner N. An ShRNA Screen Identifies MEIS1 as a Driver of Malignant Peripheral Nerve Sheath Tumors. EBioMedicine 2016; 9: 110-9.

[100] Yokoyama T, Nakatake M, Kuwata T, *et al.* MEIS1-mediated transactivation of synaptotagmin-like 1 promotes CXCL12/CXCR4 signaling and leukemogenesis. J Clin Invest 2016; 126(5): 1664-78.

[101] Roychoudhury J, Clark JP, Gracia-Maldonado G, *et al.* MEIS1 regulates an HLF-oxidative stress axis in MLL-fusion gene leukemia. Blood 2015; 125(16): 2544-52.

[102] Zhang Y, Si Y, Ma N. Meis1 promotes poly (rC)-binding protein 2 expression and inhibits angiotensin II-induced cardiomyocyte hypertrophy. IUBMB Life 2016; 68(1): 13-22.

[103] Rani L, Mathur N, Gupta R, *et al.* Genome-wide DNA methylation profiling integrated with gene expression profiling identifies PAX9 as a novel prognostic marker in chronic lymphocytic leukemia. Clin Epigenetics 2017; 9: 57.

[104] Li Q, Li J, Dai W, Li YX, Li YY. Differential regulation analysis reveals dysfunctional regulatory mechanism involving transcription factors and microRNAs in gastric carcinogenesis. Artif Intell Med 2017; 77: 12-22.

[105] Li CY, Liang GY, Yao WZ, *et al.* Identification and functional characterization of microRNAs reveal a potential role in gastric cancer progression. Clin Transl Oncol 2017; 19(2): 162-72.

[106] Abbaszadegan MR, Moghbeli M. Role of MAML1 and MEIS1 in Esophageal Squamous Cell Carcinoma Depth of Invasion. Pathol Oncol Res 2017.

[107] Mohr S, Doebele C, Comoglio F, *et al.* Hoxa9 and Meis1 Cooperatively Induce Addiction to Syk Signaling by Suppressing miR-146a in Acute Myeloid Leukemia. Cancer Cell 2017; 31(4): 549-62 e11.

[108] Cui L, Li M, Feng F, *et al.* MEIS1 functions as a potential AR negative regulator. Exp Cell Res 2014; 328(1): 58-68.

[109] Wong P, Iwasaki M, Somervaille TCP, So CWE, Cleary ML. Meis1 is an essential and rate-limiting regulator of MLL leukemia stem cell potential (vol 21, pg 2762, 2007). Genes & Development 2007; 21(22): 3017-.

[110] Chen JL, Li J, Kiriluk KJ, *et al.* Deregulation of a Hox protein regulatory network spanning prostate cancer initiation and progression. Clin Cancer Res 2012; 18(16): 4291-302.

[111] Li W, Huang K, Guo H, Cui G. Meis1 regulates proliferation of non-small-cell lung cancer cells. J Thorac Dis 2014; 6(6): 850-5.

[112] Warr MR, Pietras EM, Passegue E. Mechanisms controlling hematopoietic stem cell functions during normal hematopoiesis and hematological malignancies. Wiley Interdiscip Rev Syst Biol Med 2011; 3(6): 681-701.

[113] Kroon E, Krosl J, Thorsteinsdottir U, Baban S, Buchberg AM, Sauvageau G. Hoxa9 transforms primary bone marrow cells through specific collaboration with Meis1a but not Pbx1b. EMBO J 1998; 17(13): 3714-25.

[114] Pineault N, Abramovich C, Ohta H, Humphries RK. Differential and common leukemogenic potentials of multiple NUP98-Hox fusion proteins alone or with Meis1. Mol Cell Biol 2004; 24(5): 1907-17.

[115] Argiropoulos B, Yung E, Humphries RK. Unraveling the crucial roles of Meis1 in leukemogenesis and normal hematopoiesis. Genes Dev 2007; 21(22): 2845-9.

[116] Jones TA, Flomen RH, Senger G, Nizetic D, Sheer D. The homeobox gene MEIS1 is amplified in IMR-32 and highly expressed in other neuroblastoma cell lines. Eur J Cancer 2000; 36(18): 2368-74.

[117] Dekel B, Metsuyanim S, Schmidt-Ott KM, *et al.* Multiple imprinted and sternness genes provide a link between normal and tumor progenitor cells of the developing human kidney. Cancer Res 2006; 66(12): 6040-9.

[118] Crijns APG, de Graeff P, Geerts D, *et al.* MEIS and PBX homeobox proteins in ovarian cancer. Eur J Cancer 2007; 43(17): 2495-505.

[119] Zhu J, Cui L, Xu A, Yin X, Li F, Gao J. MEIS1 inhibits clear cell renal cell carcinoma cells proliferation and *in vitro* invasion or migration. BMC Cancer 2017; 17(1): 176.

[120] Aggarwal R, Lu J, Pompili VJ, Das H. Hematopoietic stem cells: transcriptional regulation, *ex vivo* expansion and clinical application. Curr Mol Med 2012; 12(1): 34-49.

[121] Dahlberg A, Delaney C, Bernstein ID. *Ex vivo* expansion of human hematopoietic stem and progenitor cells. Blood 2011; 117(23): 6083-90.

[122] Pietras EM, Warr MR, Passegue E. Cell cycle regulation in hematopoietic stem cells. J Cell Biol 2011; 195(5): 709-20.

[123] Barančík M, Boháčová V, Kvačkajová J, Hudecová S, Križanová Og, Breier A. SB203580, a specific inhibitor of p38-MAPK pathway, is a new reversal agent of P-glycoprotein-mediated multidrug resistance. Eur J Pharm Sci 2001; 14(1): 29-36.

[124] Wang Y, Kellner J, Liu L, Zhou D. Inhibition of p38 mitogen-activated protein kinase promotes *ex vivo* hematopoietic stem cell expansion. Stem Cells Dev 2011; 20(7): 1143-52.

[125] Zou J, Zou P, Wang J, *et al.* Inhibition of p38 MAPK activity promotes *ex vivo* expansion of human cord blood hematopoietic stem cells. Ann Hematol 2012; 91(6): 813-23.

[126] Oelke M, Maus MV, Didiano D, June CH, Mackensen A, Schneck JP. *Ex vivo* induction and expansion of antigen-specific cytotoxic T cells by HLA-Ig-coated artificial antigen-presenting cells. Nat Med 2003; 9(5): 619-24.

[127] Zheng J, Umikawa M, Zhang S, *et al. Ex vivo* expanded hematopoietic stem cells overcome the MHC barrier in allogeneic transplantation. Cell Stem Cell 2011; 9(2): 119-30.

[128] Nishino T, Wang C, Mochizuki-Kashio M, Osawa M, Nakauchi H, Iwama A. *Ex vivo* expansion of human hematopoietic stem cells by garcinol, a potent inhibitor of histone acetyltransferase. PLoS One 2011; 6(9): e24298.

[129] Walasek MA, van Os R, de Haan G. Hematopoietic stem cell expansion: challenges and opportunities. Ann N Y Acad Sci 2012; 1266: 138-50.

[130] Yu WM, Liu X, Shen J, Jovanovic O, Pohl EE. Metabolic regulation by the mitochondrial phosphatase PTPMT1 is required for hematopoietic stem cell differentiation. Metabolic regulation by the mitochondrial phosphatase PTPMT1 is required for hematopoietic stem cell differentiation. 2013.

[131] Boitano AE, Wang J, Romeo R, *et al.* Aryl hydrocarbon receptor antagonists promote the expansion of human hematopoietic stem cells. Science 2010; 329(5997): 1345-8.

[132] Peled T, Shoham H, Aschengrau D, *et al.* Nicotinamide, a SIRT1 inhibitor, inhibits differentiation and facilitates expansion of hematopoietic progenitor cells with enhanced bone marrow homing and engraftment. Exp Hematol 2012; 40(4): 342-55 e1.

[133] Li W, Li K, Wei W, Ding S. Chemical approaches to stem cell biology and therapeutics. Cell Stem Cell 2013; 13(3): 270-83.

[134] Singh KP, Garrett RW, Casado FL, Gasiewicz TA. Aryl hydrocarbon receptor-null allele mice have hematopoietic stem/progenitor cells with abnormal characteristics and functions. Stem Cells Dev 2011; 20(5): 769-84.

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