MEIS1 and its potential as a cancer therapeutic target (Review)

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Abstract. Meis homeobox 1 (Meis1) was initially discovered in 1995 as a factor involved in leukemia in an animal model. Subsequently, 2 years later, MEIS1, the human homolog, was cloned in the liver and cerebellum, and was found to be highly expressed in myeloid leukemia cells. The MEIS1 gene, located on chromosome 2p14, encodes a 390-amino acid protein with six domains. The expression of homeobox protein MEIS1 is affected by cell type, age and environmental conditions, as well as the pathological state. Certain types of modifications of MEIS1 and its protein interaction with homeobox or pre-B-cell leukemia homeobox proteins have been described. As a transcription factor, MEIS1 protein is involved in cell proliferation in leukemia and some solid tumors. The present review article discusses the molecular biology, modifications, protein-protein interactions, as well as the role of MEIS1 in cell proliferation of cancer cells and MEIS1 inhibitors. It is suggested by the available literature MEIS1 has potential to become a cancer therapeutic target.

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1. Introduction

The Meis homeobox 1 (Meis1) gene was initially discovered as a common viral integration site in the BXH-2 mouse model of leukemia in 1995 (1). Subsequently, after 2 years, the human homolog (MEIS1) was cloned in the liver and cerebellum, and was found to be highly expressed in myeloid leukemia cells (2). Two pro-viral integration clusters exist between two regions located 90 kb apart, and the MEIS1 gene alone was found between the two clusters (3). The MEIS1 gene encodes a 3.8 kb transcript with an open reading frame that encodes a homeodomain protein (4).

Homeobox protein MEIS1 belongs to the three amino acid loop extension (TALE) homeodomain transcription factor family, whose members also include MEIS2 and MEIS3 (5). MEIS2 protein comprises of 477 amino acids and has a molecular weight of 51,790 Da. This protein is coded by the MEIS2 gene, that has a length of 212,108 bp. The MEIS3 protein is coded by the MEIS3 gene with a length of 19,110 bp and is composed of 375 amino acids. The potential interplay between the two proteins and MEIS1, is illustrated in Fig. 1 (modified from www.string-db.org).

MEIS1 is involved in a number of physiological and pathophysiological processes; most notably, in cell migration, apoptosis and metabolism. The present review article summarizes the results of previous studies that have implicated MEIS1 in cancer cell proliferation. The potential use of MEIS1 as a novel biomarker and therapeutic target in cancer was also discussed.

2. Molecular biology of MEIS1

DNA/RNA. MEIS1 is located between LOC729348 and LOC100507073 on chromosome 2p14, and contains the anonymous markers, D2S134 and NIB1519 (2,6). It consists of 13 exons and 137,360 bp (6). The 3’ untranslated region (3’ UTR) of MEIS1 is highly conserved during evolution (7). The structure of the MEIS1 gene is illustrated in Fig. 2. In total, four MEIS1 isoforms, produced by alternative splicing, have been described: MEIS1a, MEIS1b, MEIS1c and MEIS1d (6). MEIS1a possesses all 13 exons, whereas MEIS1b lacks the 95-bp exon 12 (4). MEIS1c lacks 49 amino acids (Val 162 to Gln 210) and is expressed in mouse embryos (8). MEIS1d lacks exon 8 and is expressed in mouse colorectal cancer cells (9).
A linear diagram of MEIS1 isoforms with their exons is presented in Fig. 3.

The full-length MEIS1 mRNA consists of 3,198 bp (6). The expression of MEIS1 mRNA in different human tissues, according to the Human Protein Atlas (http://www.protein-atlas.org/), is illustrated in Fig. 4. The highest expression levels of MEIS1 mRNA are found in the endometrium, fallopian tubes and smooth muscle, whereas the lowest levels are found in skeletal muscle, liver and bone marrow.

**Protein.** Full-length MEIS1 consists of 390 amino acids and has a molecular weight of 43,016 Da (6). MEIS1 contains a pre-B-cell leukemia homeobox (PBX)1 interaction domain, serine/threonine-rich domain, aspartic acid/glutamic acid-rich domain, poly-aspartic acid domain, homeodomain and transcriptional activation domain (10). The conserved PBX interaction motif, homeodomain and C-terminal region are critical for leukemic transformation (11).

MEIS1 is localized mainly in the nucleus (12), although its expression has also been detected in the cytoplasm in certain tumor cells, such as in ovarian cancer cells (13). During pregnancy, MEIS1 localizes to the cytoplasm and the membrane of endometrial glandular epithelial cells (14).

Relative MEIS1 expression at the protein level in different human tissues, according to the Human Protein Atlas, is illustrated in Fig. 5. The highest expression of MEIS1 occurs in the fallopian tubes and smooth muscle. However, a previous study suggested that MEIS1 was expressed at highest levels in the endo- and myometrium among 87 types of normal tissues (15).

In addition to the pathological state, other factors such as cell type, age and environmental conditions also affect MEIS1 expression. MEIS1 is highly expressed in all cell lines with a mixed-lineage leukemia (MLL) mutation, but not in wild-type MLL cell lines (16). The expression of MEIS1 in solid tumors is somewhat paradoxical, as it is overexpressed in certain tumor types, whereas it is downregulated in others (5). The cell types from different organ sites under investigation (5) and the types of metabolism (10) the cancer cells require may be responsible for these contradicting findings. MEIS1 tends to be expressed at higher levels in fetal hearts than in adult hearts (17); however, another study reported a lower MEIS1 expression in postnatal hearts than in adult hearts (18). Among pediatric patients with acute lymphoblastic leukemia (ALL), MEIS1 expression is more frequent in infant ALL than in childhood ALL (19). Discrepancies among these studies, particularly, the association of MEIS1 with age, requires further investigation. Hypoxia has been shown to reduce the expression of MEIS1 in the heart (20), and to downregulate MEIS1 expression in pulmonary artery smooth muscle cells in both primary culture and animals (21).

### 3. Modification

MEIS1 related modifications include DNA methylation and protein ubiquitination. These are discussed below.

**DNA methylation.** The hypomethylation of the MEIS1 promoter mediated by DNA methyltransferase 3A (DNMT3A) has been observed in acute myeloid leukemia (AML) without MLL fusions (22). In AML involving the AML-RUNX1 partner transcriptional co-repressor 1 (ETO) fusion, the hypermethylation of the MEIS1 promoter causes the transcript level to decrease with time (23). MEIS1 downregulation can be reversed by the combination of the demethylating agent, decitabine, and the histone deacetylase inhibitor, trichostatin A (23). Although no methylation of the MEIS1 promoter has been observed in patients with AML (24), trimethylation mediated by SET domain bifurcated histone lysine methyltransferase 1 (SETDB1) or the complex of polymerase-associated factor 1 (PAF1) and SETDB1 (25), has been detected. Thus, modifications of the MEIS1 gene differ across types of AML. MEIS1 gene methylation has also been observed in solid tumors, such as bladder cancer (26). The methylation level of the MEIS1 promoter is significantly associated with MEIS1 downregulation in the B-raf proto-oncogene (BRAF)p.v600e mutant human colon cancer tissues and colon cancer cell lines (27). However, another study using colorectal cancer tissues from 42 patients failed to detect the methylation of the MEIS1 promoter (28).

**Ubiquitination.** Protein ubiquitination promotes its degradation (29). The exposure of hematopoietic stem cells to branched-chain amino acid (BCAA) has been shown to
increase the cell division cycle 20 (CDC20)-mediated ubiquitination of MEIS1 protein (30). Conversely, the competitive inhibition of E3 binding to MEIS1 by PBX3 prevents the ubiquitination of MEIS1 (31).

4. Protein-protein interactions

Protein-protein interactions play crucial roles in cellular functions and biological processes. MEIS1 is known to interact with several partners, including homeobox (HOX) and PBX proteins.

**HOX protein family.** MEIS1 binds to HOXA9 to form a heterodimeric complex (32), which in turn binds to target DNA sequences that contain the MEIS1 binding site (TGACAG) and an AbdB-like HOX site (TTTTACGAC) (33). HOXA10, HOXA11, HOXD12 and HOXB13 can also form DNA-binding complexes with MEIS1b (33). In mouse embryos, both HOXA13 and HOXD13 interact with MEIS1a C-terminal domain (18 amino acids) and MEIS1b C-terminal domain (93 amino acids) (34). HOX protein stabilizes the interaction between MEIS1 and its target DNA; as a result, target DNA dissociates at a markedly slower rate from the MEIS1-HOX complex than from MEIS1 alone (33). The overexpression of MEIS1 induces cell apoptosis through caspase-dependent processes, whereas the overexpression of MEIS1 and HOXA9 inhibits apoptosis and protects cells from the influence of apoptosis-inducing factors (35).

MEIS1 and HOX can also bind to a third protein to form trimers. For example, MEIS1 forms a trimer with HOXA9 and PBX2 in myeloid leukemia cells, which then binds to the target DNA (36). Trimers formed by MEIS1, HOXA10 and PBX2 mediate the expression of target genes in the human endometrium (37).

**PBX protein family.** PBX proteins located in the nucleus are significantly associated with MEIS1 expression (38). PBX1 and MEIS1 form a dynamic dimer, with each protein binding to its respective target DNA site (39). A cyclic adenosine monophosphate (cAMP)-responsive sequence (CRS1) in the bovine cytochrome P450 family 17 (CYP17) gene is a transcriptional regulatory element that contains binding sites for PBX and MEIS1. PBX1 and MEIS1 bind cooperatively to CRS1 to regulate cAMP-dependent transcription, whereas neither protein can bind this element on its own (40). The dimers formed by PBX1 and MEIS1 can also bind to the PBX/MEIS binding site in the SRY-box transcription factor 3 (SOX3) promoter, where they regulate SOX3 expression during development (41).

**PBX-regulating protein-1 (PREP1)** controls the expression of MEIS1 through post-transcriptional regulation: PREP1 inhibits the interaction between PBX1 and MEIS1 in mouse embryonic fibroblasts, destabilizing MEIS1 and inhibiting the interaction between MEIS1 and DEAD-box helicase 3 x-linked (DDX3x) and DDX5, and ultimately decreasing MEIS1 tumorigenicity (42). Dimerization with PBX3 stabilizes MEIS1, allowing it to upregulate target genes, such as FMS related receptor tyrosine kinase 3 (FLT3) and tribbles pseudokinase 2 (TRIB2), thereby enhancing HOX9-mediated transformation. MEIS1 protein that does not bind to PBX3 is prone to ubiquitination and subsequent degradation. Mutations in the PBX binding region in MEIS1 can also prevent the ubiquitination of MEIS1, as PBX3 and the responsible E3 ubiquitin ligase share common binding requirements within MEIS1 (30,43).

MEIS1 can form trimers with PBX protein, as well as HOX protein. MEIS1 in megakaryocytes binds to PBX1b and PBX2 to form MEIS1/PBX complexes, which then binds to the TGACAG sequence in tandem repeats of the MEIS1 binding element (TME) of the platelet factor 4 (PF4) promoter, inducing the expression of the gene. The simultaneous overexpression of MEIS1 and PBX2 potentiates the activation of the PF4 promoter, and is abrogated when the MEIS1 binding site on the TME is destroyed (44).

5. Role of MEIS1 in the proliferation of cancer cells

As a transcription factor, MEIS1 functions as a positive regulator of the proliferation of leukemia cells (45), as well as in certain solid tumors, such as esophageal squamous cell carcinoma (46), malignant peripheral nerve sheath (47) and Ewing sarcoma (48); however, it has also been shown to function as a
negative regulator of several other solid tumors (49) (Fig. 6 and Table 1). A schematic diagram of the promoting and inhibitory roles of MEIS1 in various types of cancer is presented in Fig. 6.

**Leukemia.** MEIS1 interacts with a variety of partners to promote the proliferation of leukemia cells. Recent studies have demonstrated that MEIS1 interacts with HOXA9 to promote cell proliferation in leukemia via synaptotagmin-like 1 (SYTL1) (50), cyclin D3 (CCND3) (51) or spleen tyrosine kinase (Syk) (52). In patients with acute AML, the interaction between MEIS1 and HOXA9 induces the proliferation of leukemia cells via the simultaneous overexpression of MEIS1 and HOXA9 (31,52,53), suppresses granulocyte colony-stimulating factor (G-CSF)-induced granulocytic differentiation and promotes cell proliferation via stem cell factor (SCF) (54). In addition, the complex formed by MEIS1 and HOXA9 is recruited to the FLT3 promoter to turn on the gene (55), and FLT3 induces mitogen-activated protein kinase (MAPK) phosphorylation, inhibits apoptosis and promotes leukemia cell proliferation (56). The MEIS1-HOXA9 complex also interacts with TRIB1 to induce MAPK phosphorylation, and to stimulate leukemia cell proliferation (57). A recent study demonstrated that the MEIS1-HOXA9 complex bound to the endothelin receptor type A (EDNRA, a tumor promotor) promoter in leukemia cells, resulting in cell proliferation and in resistance to apoptosis (58). HOXD13 also helps regulate the pro-proliferative function of MEIS1 in AML. The human leukemia-specific fusion gene NUP98-HOXD13 (ND13) has myeloproliferative activity, although it does not directly induce AML in mice (59). However, when MEIS1 expression is upregulated, ND13 can induce cell proliferation and generate AML in transplanted mice (59). PBX also functions as a cofactor of MEIS1 to regulate leukemia cell proliferation. Immortalized progenitor cells induced by HOXA9 typically do not undergo leukemic transformation; however, the co-expression of MEIS1 and PBX can induce FLT3 expression, increase MAPK phosphorylation and promote leukemic transformation (60). The co-expression of MEIS1 and PBX3 can transform normal hematopoietic stem/progenitor cells in vitro and induce AML (leukemia cell proliferation) in mice (61). MEIS1 is also involved in MLL. MEIS1 regulates the differentiation arrest, cycle activity, in vivo invasion and self-renewal of MLL cells, and thus represents a key limiting factor of MLL stem cell potential (62). The downregulation of MEIS1 and HOXA alters...
C-X-C motif chemokine receptor 4 (CXCR4)/stromal cell derived factor 1 (SDF-1) signaling to inhibit the proliferation of transplanted mutant MLL-rearranged acute leukemia cells (63), again supporting a pro-proliferative role of MEIS1 in MLL.

Solid tumors. MEIS1 has been associated with a variety of solid cancers, including prostate, non-small cell lung and gastric cancer, as well as clear cell renal cell carcinoma, esophageal squamous cell carcinoma, malignant peripheral nerve sheath tumors and Ewing sarcoma. The MYC-mediated downregulation of MEIS1 upregulates the androgen receptor (AR) to promote prostate cancer cell proliferation (64). AR transcription is inhibited by the overexpression of MEIS1 and is promoted by MEIS1 knockdown with small interfering RNA (49). A proposed mechanism is that MEIS1 interacts with AR to affect the trafficking of androgen between the cytoplasm and nucleus. In this manner, MEIS1 may inhibit prostate cancer cell proliferation by regulating AR, since this receptor plays a key role in proliferation of human prostate cancer cells. MEIS1 also participates in prostate cancer through mechanisms independent of AR. Recent studies have indicated that MEIS1 regulates the proliferation of prostate cancer cells by interacting with MEIS-interacting domains in HOXA9 (65), which induces decorin (DCN), a multi-RTK inhibitor (66). MEIS1 knockdown has been shown to significantly increase the proliferation of non-small cell lung cancer cells through a mechanism related to DNA synthesis and histone H3 phosphorylation (67).

Table I. Roles of MEIS1 in cancer cell proliferation.

| Disease                        | Cell type                        | MEIS1 expression | Role of MEIS1 in proliferation | MEIS1 interacting partner | (Refs.) |
|--------------------------------|----------------------------------|------------------|-------------------------------|--------------------------|---------|
| Leukemia                       | H9M1                             | ↑                | Promote                       | HOXA9                    | (50)    |
| Leukemia                       | Bone marrow cell lines           | ↑                | Promote                       | -                        | (51)    |
| Leukemia                       | Myeloid progenitors              | ↑                | Promote                       | HOXA9                    | (52)    |
| Leukemia                       | Myeloid clonogenic progenitor    | ↑                | Promote                       | HOXA9                    | (32,53) |
| Leukemia                       | Bone marrow progenitors           | ↑                | Promote                       | HOXA9                    | (54)    |
| Leukemia                       | Hematopoietic progenitors         | ↑                | Promote                       | HOXA9                    | (55)    |
| Leukemia                       | Primary leukemia cells            | ↑                | Promote                       | HOXA9                    | (57)    |
| Leukemia                       | Bone marrow cell lines           | ↑                | Promote                       | HOXA9                    | (58)    |
| Leukemia                       | Myeloid clonogenic progenitor    | ↑                | Promote                       | -                        | (59)    |
| Leukemia                       | Hematopoietic progenitors         | ↑                | Promote                       | PBX                      | (60)    |
| Leukemia                       | Hematopoietic stem/progenitor cells| ↑            | Promote                       | PBX3                     | (61)    |
| Leukemia                       | Precursor B-cell leukemic line, RS4 | ↑                | Promote                       | -                        | (63)    |
| Prostate cancer                | Human prostate cancer cells       | ↓                | Inhibit                       | -                        | (49)    |
| Prostate cancer                | Human prostate cancer cells, LNCaP| ↓                | Inhibit                       | -                        | (64)    |
| Prostate cancer                | Human prostate cancer cells, DU145 | ↑              | Promote                       | HOXB13                   | (65)    |
| Prostate cancer                | Human prostate cancer cells, DU145 | ↓              | Inhibit                       | HOXB13                   | (66)    |
| Non-small cell lung cancer     | A549 cells                       | ↓                | Inhibit                       | -                        | (67)    |
| Gastric cancer                 | Human GC cell line, MKN28         | ↓                | Inhibit                       | -                        | (68)    |
| Clear cell renal cell carcinoma| Human ccRCC cell lines, 786-O or | ↓                | Inhibit                       | -                        | (69)    |
| cancer                          | Caki-1                           |                  |                               |                          |         |
| Esophageal squamous cell cancer| Human KYSE-30 ESCC cells          | ↑                | Promote                       | SOX2                     | (46)    |
| Esophageal squamous cell cancer| Human KYSE-30 ESCC cells          | ↑                | Promote                       | -                        | (70)    |
| Malignant peripheral nerve sheath| MPNST cell line, STS26T           | ↑                | Promote                       | -                        | (47)    |
| Ewing sarcoma                  | Ewing sarcoma cell lines, A673, SKNMC and TC32 | ↑ | Promote                       | -                        | (48)    |

MEIS1, Meis homeobox 1; HOXA9, homeobox A9; PBX, pre-B-cell leukemia homeobox; SOX2, SRY-box transcription factor.
Table II. Basic information about MEIS1 inhibitors.

| Name/code       | Chemical structural formula | Type of MEIS1 inhibited action | Effect                                                                                           | (Refs.) |
|-----------------|-----------------------------|--------------------------------|--------------------------------------------------------------------------------------------------|---------|
| MI-2            | ![MI-2 chem structure]      | Indirect                       | Anti-proliferative effects in MLL cells                                                          | (71)    |
| MI-503          | ![MI-503 chem structure]    | Indirect                       | Inhibitory effects on MLL cells                                                                   | (72)    |
| MI-3454         | ![MI-3454 chem structure]   | Indirect                       | Anti-proliferative effect in acute leukemia cells and primary patient samples with MLL1 translocations or NPM1 mutations | (74)    |
| Compound 9e     | ![Compound 9e chem structure] | Indirect                       | Anti-proliferative activities against leukemia cells                                              | (80)    |
| CCI-007         | ![CCI-007 chem structure]   | Indirect                       | Cytotoxic activity against infant leukemia in MLL-r                                               | (81)    |
| MEISi-1         | ![MEISi-1 chem structure]   | Direct                         | Modulated activity in hematopoietic stem cell via inhibiting MEIS1 directly                       | (82)    |
| MEISi-2         | ![MEISi-2 chem structure]   | Direct                         | Anti-proliferative activity in hematopoietic stem cell via inhibiting MEIS1 directly              | (82)    |

MEIS1, Meis homeobox 1; MLL, mixed-lineage leukemia; NPM1, nucleophosmin 1; MLL-r, mixed-lineage leukemia-rearranged; MLL-FPs, mixed-lineage leukemia-fusion proteins.

Marker of cell proliferation (70). In malignant peripheral nerve sheath tumors, MEIS1 expression is increased and promotes cell proliferation and maintains cell survival by inhibiting the cell cycle suppressor, p27, via transcription factor inhibitor of DNA binding 1 (ID1) (47). In Ewing sarcoma, MEIS1 collaborates with EWS-FLI1 to stimulate cell proliferation (48).
6. MEIS1 inhibitors

Since MEIS1 plays an important pro-proliferative role in leukemia and certain solid tumors, it has the potential for use as a therapeutic target. MEIS1 inhibitors under development for treatment of cancer are reviewed and listed in Table II.

Menin-MLL inhibitors have an anti-proliferative function via MEIS1 in leukemia cells. MI-2 is a first-generation small molecule inhibitor of the Menin-MLL interaction, but has poor pharmacological profiles (71). The second-generation inhibitor, MI-503, is highly potent and orally bioavailable, and has been shown to exert profound anti-proliferative effects in MLL cells (72). The cytotoxic concentration of these compounds in cells was >2 µM and the relatively modest effect in vivo suggested limited druggability (73). The third generation inhibitor, MI-3454, is well-tolerated and does not impair normal hematopoiesis in mice; however, it inhibits the proliferation and induces the differentiation of acute leukemia cells by downregulating MEIS1 and FLT3 indirectly (74). VTP-50469, another type of highly selective oral Menin-MLL inhibitor, appears to promote leukemia cell differentiation and inhibit cell proliferation through the indirect downregulation of MEIS1 (75-77). All Menin-MLL inhibitors mentioned above are reversible in nature. To achieve an optimal anti-leukemic activity, extended drug exposure is required (78). M-525, a highly potent and irreversible Menin-MLL inhibitor, has been shown to inhibit the proliferation of and suppress MEIS1 expression in MLL cells at a sub-nanomolar concentration (78), indicating that the downregulation of MEIS1 with Menin-MLL inhibitors may represent a promising therapeutic strategy for MLL. In addition to Menin-MLL inhibitors, certain other agents that downregulate MEIS1 indirectly can exert anti-proliferative effects in leukemia cells. For instance, the proton pump inhibitor, rabeprazole, selectively suppresses the proliferation and induces the apoptosis of leukemia cells harboring MLL fusion proteins by downregulating MEIS1 (79). The DOT1-like histone lysine methyltransferase (DOTIL) inhibitor compound, 9e (80), and the MLL-rearranged leukemia inhibitor, CCI-007 (81), also produce similar effects via MEIS1-dependent mechanism.

In a recent study, two small molecule MEIS1 inhibitors (MEISi-1 and MEISi-2) were identified using high-throughput in silico screening, and induced hematopoietic stem cell expansion (82).

7. Conclusions and future perspectives

The present review article summarized the characteristics of MEIS1, its role in cancer cell proliferation and the current status on the development of MEIS1 inhibitors as therapeutic agents. MEIS1 is upregulated and mediates cell proliferation in leukemia and certain solid tumors (e.g., esophageal squamous cell carcinoma and malignant peripheral nerve sheath tumors), whereas it inhibits cell proliferation in other solid tumors. Agents that inhibit MEIS1 directly or indirectly are being developed. MEIS1 is increasingly recognized as a marker of cancer diagnosis and a therapeutic target.

The paradoxical role of MEIS1 among solid tumors (stimulatory in some but inhibitory in others) warrants further investigation. Illustrating the potential association between the Warburg effect, cancer cell proliferation and MEIS1 may resolve this contradiction, as the Warburg effect plays an important role in cell proliferation (83). Designing MEIS1 inhibitors based on the molecular structure of MEIS1 may expedite the developmental process of anticancer agents.

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Authors' contributions

MY drafted the manuscript. ZC conceived the study and participated in the manuscript preparation. ZY and KZ assisted in the literature search and edited the manuscript. YG revised the manuscript. ZC and MY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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