Oncogenic mechanisms and therapeutic potential of SALL4 in hematological malignancies (Review)

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Abstract. As a member of the spalt like transcription factor (SALL) family, SALL4 regulates multiple oncogenic processes including cell proliferation, metastasis, epithelial-mesenchymal transition, cancer stem cell maintenance and drug resistance. Physiologically, it is essential for the self-renewal of embryonic and hematopoietic stem cells. Aberrant upregulation of SALL4 is frequently observed in both solid tumors and hematological malignancies; it has been proven to play a critical role in hematological malignancies, especially acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, chronic myeloid leukemia and mixed-lineage leukemia, where it promotes malignant cell proliferation, disease progression, and chemoresistance via downstream genes and key signaling pathways. Targeting key oncogenic molecules represents a promising therapeutic strategy for hematological malignancies. Elucidating the regulatory mechanisms of SALL4 may identify a novel therapeutic target. The present review summarizes the regulatory functions of SALL4 on key oncogenic targets and its upregulation profile in hematological malignancies. Although some mechanisms are mainly illustrated in solid tumors, they provide important insights for hematological cancer. Overall, SALL4 exhibits great potential as a novel therapeutic target and prognostic biomarker for hematological malignancies.

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1. Introduction

Spalt like transcription factor 4 (SALL4), a member of the human SALL transcription factor family (SALL1-4) that originates from the drosophila spalt gene, is encoded on chromosome 20q13 and exists in two primary isoforms (SALLA and SALLB) (1-4). As a zinc-finger (ZF) transcription factor, SALL4 contains multiple C2H2-ZF domains that mediate its gene regulatory functions (5). Functioning as a critical stem cell regulator, SALL4 is essential for maintaining the proliferative capacity and directing the differentiation of both embryonic stem cells (ESCs) and hematopoietic stem cells (HSCs). For ESCs, SALL4 cooperates with core pluripotency factors, including OCT4, SOX2 and NANOG, to sustain self-renewal and maintain pluripotent states (6-9). Besides existing in ESCs, SALL4 expression is also maintained in adult stem cell populations. The oncogenic potential of SALL4 was first demonstrated in 2006, when it was initially characterized as a cancer-promoting gene (10). Dysregulated SALL4 expression has been linked to numerous solid tumors; it is expressed in Wilms tumor, hepatocellular carcinoma, gastric cancer and breast, ovarian and testicular germ cell tumors (11,12). Regarding HSCs, physiological SALL4 expression in bone marrow shows a distinct pattern; SALL4 is enriched in HSCs but markedly reduced upon lineage commitment (13). Loss of SALL4 expression is correlated with CD34 downregulation in HSCs, while SALL4-expanded HSCs show markedly improved *in vivo* repopulation efficiency following syngeneic transplantation (14). This indicates the vital stemness effect of SALL4 in hematopoiesis. However, if SALL4 is upregulated, the function of normal hematopoiesis is impaired, leading to malignant hematopoiesis. Milanovich *et al* (15) found that genetic overexpression of either SALL4A or SALL4B in primitive hematopoietic populations inhibits clonogenic potential *in vitro*. SALL4B-overexpressing lineage-depleted bone marrow cells completely lost their engraftment potential and showed no evidence of hematopoietic reconstitution in recipient mice. A number of experiments have demonstrated upregulated SALL4 throughout all courses of some hematological malignancies, including onset, evolvement, poor prognosis and drug resistance (5). For these reasons, summarizing the mechanism of

SALL4 in hematological malignancies can help target SALL4 so that effective therapy breakthroughs can be explored in the future.

2. Downstream effects of SALL4 in tumors

Yang *et al* (16) used genome-wide chromatin immunoprecipitation analysis to identify the complete repertoire of SALL4 binding sites across the genome, and identified >2,000 high-confidence SALL4-binding loci in NB4 acute promyelocytic leukemia cells, revealing its extensive transcriptional regulatory network. SALL4 downregulates apoptosis-inducing genes [phosphatase and tensin homolog (PTEN) and tumor protein p53 (p53)] and inflammatory factors [tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ)], and upregulates apoptosis-inhibiting genes [B-cell-specific Moloney murine leukemia virus integration site 1 (Bmi-1) and B-cell lymphoma-2 (BCL-2)], cell cycle-related genes [cellular myelocytomatosis oncogene (c-Myc) and Cyclin D] and transcription factors [homeobox A9 (HOXA9)]. These downstream molecules of SALL4 and mediate SALL4-driven stemness and malignant proliferation of leukemic cells.

Apoptosis-inducing genes

PTEN. PTEN-PI3K-PKB/AKT inhibits tumor cell proliferation and maintains stem cell self-renewal by regulating cell cycle and metabolism. PTEN, a critical tumor suppressor encoded at 10q23.31 (17), serves as a master regulator of diverse cellular functions including cell motility and polarity control, metabolic and proliferative signaling, stem cell maintenance and differentiation, cytoskeletal organization and microenvironment interactions. PTEN possesses both protein and lipid phosphatase activity. The lipid phosphatase activity is intimately linked to the ability of PTEN to function as a tumor suppressor (18). Garcia-Cao *et al* (19) discovered the suppressive effect of PTEN in tumor metabolism. PTEN reduces glutaminolysis and the Warburg effect (20), a metabolic role primarily established in solid tumors. PI3K converts phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2] to phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P3]. PI(3,4,5)P3 recruits a number of pleckstrin homology domain-containing proteins, including AKT/PKB and its activating kinase, 3-phosphoinositide-dependent protein kinase-1. PI3K-PI(3,4,5)P3-AKT/PKB promotes glycolysis by mechanisms that include the expression of glucose transporters and by regulating glycolytic pathway enzymes via phosphorylation (21-23). AKT can also activate mechanistic target of rapamycin by stimulating hypoxia-inducible factor-1α, which drives tumor cells to switch from oxidative phosphorylation to glycolysis in tumorigenesis (24,25). These metabolic mechanisms remain largely speculative in hematological malignancies. PTEN catalytically removes the phosphate group from PI(3,4,5)P3, increasing PI(4,5)P2 concentration, which blocks the recruitment and activation of PKB/AKT, inhibiting a series of downstream effects (26). Rapidly proliferating cancer cells escape the deregulation of the cell cycle progression through G1-S transition. PI3K-PKB/AKT promotes cell cycle progression into S phase by regulating several different proteins (27). The role of the PTEN-PI3K/AKT axis in regulating the cell cycle has been well-documented in HSCs; activation of PI3K triggers downstream AKT signaling, promoting cell proliferation. Conversely, PTEN-mediated suppression of this pathway helps maintain HSC quiescence and supports their long-term self-renewal capacity (28,29). This is one of the best validated functions in the hematopoietic system.

SALL4 acts as a PTEN inhibitor, suppressing PTEN-mediated dephosphorylation of phospho-AKT. In cells with high SALL4 expression, this enhances PI3K-dependent survival signaling and blocks apoptosis by sustaining elevated phospho-AKT levels. Notably, this effect can be reversed using an inhibitory peptide, but the pro-survival phenotype is restored upon PTEN inhibition, further reinforcing PI3K/AKT-driven cell survival and anti-apoptotic activity (30,31). This SALL4-PTEN-AKT survival pathway is confirmed in leukemia models. SALL4 collaborates with a nucleosome remodeling and deacetylase (NuRD) complex component, histone deacetylase 2 (HDAC2), to bind and epigenetically silence the PTEN promoter, indicating that SALL4-mediated PTEN repression occurs through NuRD-dependent histone deacetylation (32,33). SALL4-NuRD interactions are validated in hematopoiesis, but the full axis remains mostly studied in solid tumors. Histone acetylation relaxes chromatin into transcription-permissive euchromatin, thereby boosting gene transcription. The NuRD complex possesses two key epigenetic functions: histone deacetylation and ATP-fueled nucleosome rearrangement. In contrast, histone deacetylation drives chromatin compaction into silent heterochromatin and silences target gene transcription. By interacting with sequence-specific DNA-binding factors, SALL4 mediates transcriptional repression during embryonic stem cell maintenance, organismal development, hematopoietic differentiation and tumor progression, involved in various tumor progressions (34). SALL4 can bind to HDAC1 and HDAC2, silencing the transcription of PTEN. The NuRD complex consists of seven core components, chromodomain helicase DNA binding protein (CHD3/4), HDAC1/2, retinoblastoma binding protein (RBBP4), metastasis-associated protein 1 (MTA1) and methyl-CpG binding domain protein, among which RBBP4 serves as a critical subunit. RBBP4 is frequently upregulated in various cancer types, such as acute myeloid leukemia (AML) and hepatocellular carcinoma (35-37). SALL4 recruits the NuRD complex (HDAC2, CHD3/4 and MTA1/2) through its N-terminal 12-residue motif, directly occupies the PTEN promoter and inhibits its transcription. SALL4 transgenic mice exhibit myeloid leukemia features with persistently reduced PTEN expression (32). Dysregulation of the SALL4-RBBP4/NuRD axis epigenetically silences the tumor suppressor PTEN, leading to constitutive PI3K/AKT pathway activation. This aberrant signaling promotes cancer cell survival and contributes to therapy resistance (38,39). This complete signaling cascade is established in solid tumors and remains to be fully validated in blood cancer. The underlying mechanisms are summarized in Fig. 1.

p53. p53, known as the 'genome guardian', plays a vital role in inducing apoptosis; it activates the transcription of genes involved in cell cycle inhibition, DNA repair, senescence, apoptotic pathways and cellular differentiation to ensure genomic stability across various cell types (40). In the blood system, p53 accelerates hematopoietic stem and progenitor cell (HSPC) and HSC physiological aging and can

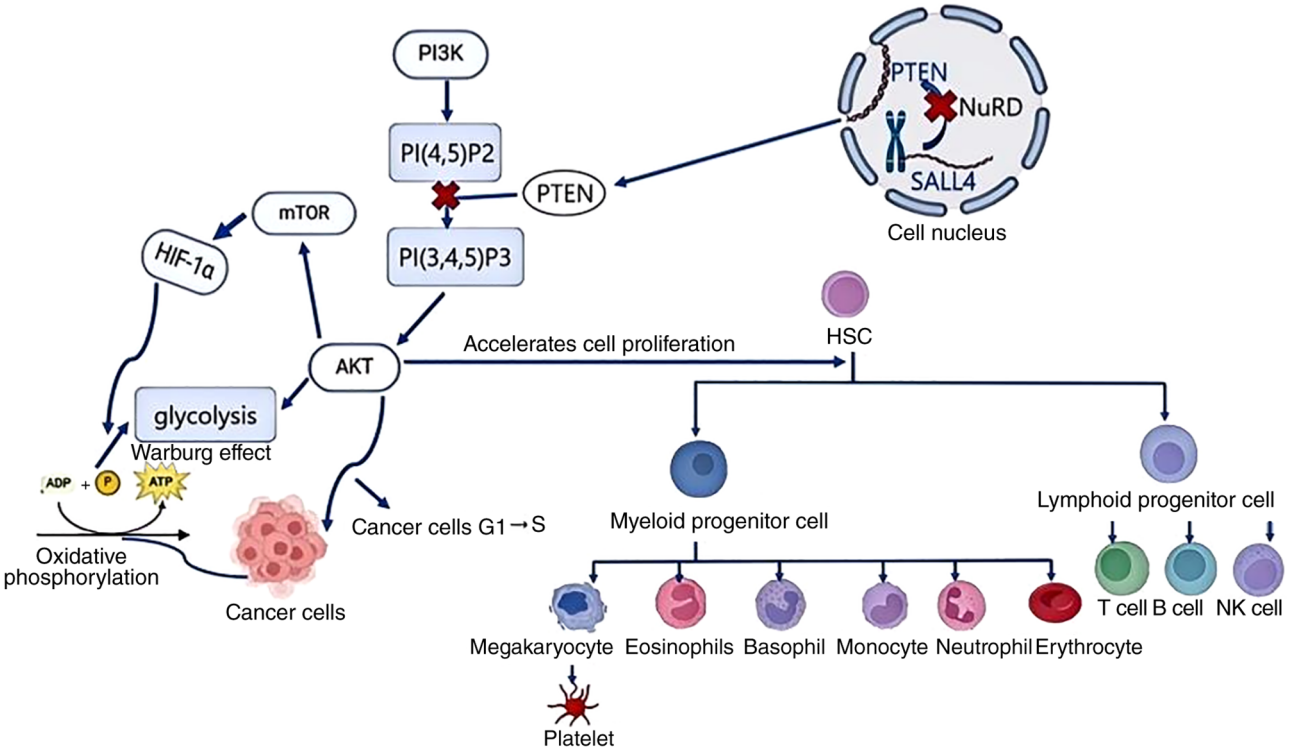


Figure 1. SALL4 upregulates the PI3K-PIP3-AKT/PKB pathway through inhibiting PTEN. SALL4 represses PTEN through the epigenetic repressor, NuRD; PTEN catalytically removes PI(3,4,5)P3 to produce PI(4,5)P2 inhibiting the PI3K-PIP3-AKT/PKB pathway; the PI3K-PIP3-AKT/PKB pathway accelerates the proliferation of HSCs; the PI3K-PIP3-AKT/PKB pathway promotes cell cycle progression from G1 into S phase; AKT can activate mTOR stimulating HIF-1α, which switches from oxidative phosphorylation to glycolysis in tumorigenesis stimulating the Warburg effect in cancer cells. HIF-1α, hypoxia-inducible factor-1a; HSCs, hematopoietic stem cells; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PI(3,4,5)P3, phosphatidylinositol 3,4,5-trisphosphate; PI(4,5)P2, phosphatidylinositol 4,5-bisphosphate; NK, natural killer; NuRD, nucleosome remodeling and deacetylase; SALL4, spalt like transcription factor.

be used to identify human AMLs with adverse survival (41). Myeloid cell leukemia-1 (MCL-1), an anti-apoptotic BCL-2 family protein, suppresses apoptosis in hematological malignancies by binding and neutralizing proapoptotic factors. This interaction promotes cell survival and confers resistance to conventional chemotherapies and molecularly targeted treatments (42). Through suppression of the oncogenic Ras/MAPK pathway and concomitant activation of GSK-3, p53 facilitates post-translational modification and subsequent proteasomal degradation of MCL-1. This molecular mechanism markedly contributes to p53-mediated tumor suppression (43). Reciprocal regulation between p53 and PTEN maintains genomic stability through multilayered crosstalk. As a transcription factor, p53 activates PTEN transcription by binding its promoter. In turn, PTEN stabilizes p53 via both phosphatase-dependent and -independent pathways. Through phosphatase activity, PTEN suppresses PI3K/AKT signalling to inhibit MDM2-driven p53 degradation. Independently of its catalytic function, PTEN physically interacts with p53 to increase p53 stability and DNA-binding capacity (44). Dysregulation of this PTEN-p53 feedback loop promotes malignant progression in haematological malignancies. Notably, SALL4 can interfere with this PTEN-p53 tumour-suppressive network at multiple levels: SALL4 epigenetically represses PTEN transcription, and it also indirectly impairs p53 function by targeting upstream p53 regulators. In AML, SALL4 indirectly downregulates p53 activity by repressing p14 alternative reading frame (p14ARF), an upstream regulator of the p53 pathway, thereby inhibiting apoptosis and promoting the survival of AML cells (45). The relevant mechanisms are summarized in Fig. 2.

Inflammatory factors

TNF-α. TNF is a central regulator of immunity; it is also a key factor in tumor inhibition. TNF is an activator of NF-κB, a critical pathway that enhances survival in various immune cells. In monocytes and macrophages, this anti-apoptotic mechanism contributes to their tumor-resistant properties through innate immune functions (46). TNF regulates cellular processes such as apoptosis, survival and proliferation through two distinct cell membrane receptors, TNF receptor (TNFR) 1 and 2, although the precise molecular mechanisms underlying these cellular responses remain unclear. However, under normal physiological conditions, TNFR signaling does not induce apoptosis in monocytes or macrophages, as TNF-mediated activation of the NF-κB transcription pathway promotes the expression of anti-apoptotic genes; therefore, NF-κB is important in monocyte and macrophage protection (47-50). Exosomes can transport the non-coding RNA microRNA (miR)-146a-5p into macrophages, where it modulates their cytokine secretion profile and suppresses antigen-presenting capacity by downregulating TNF-α expression while enhancing inhibitory receptor signaling, including programmed death ligand 1 (PD-1) and cytotoxic-T-lymphocyte-antigen-4 (CTLA-4) (51). The underlying mechanisms are summarized in Fig. 3. In AML and myelodysplastic syndrome (MDS) cells, SALL4

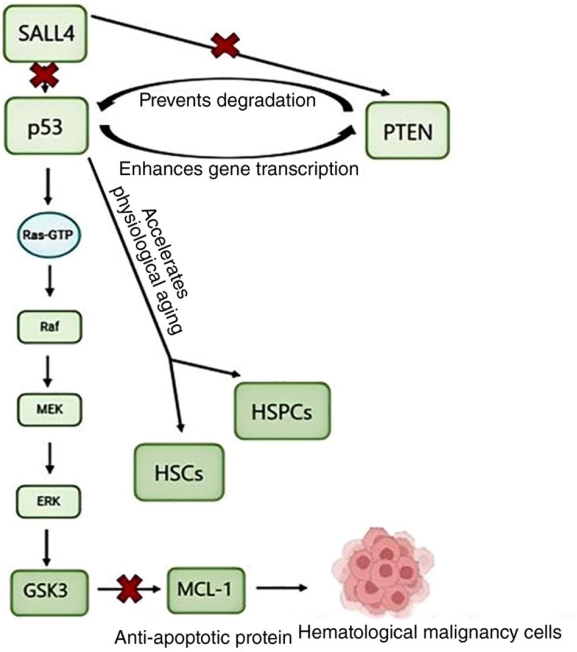


Figure 2. SALL4 inhibits p53 through governing the binding of p53 to enhancers. p53-mediated activation suppresses the Ras/Raf/MEK/ERK pathway and induces GSK-3 activation. GSK-3 in turn modulates MCL-1 phosphorylation and promotes MCL-1 degradation, consequently exerting antitumor effects; p53 binds to the PTEN promoter and enhances PTEN gene transcription; PTEN can stabilize p53 by phosphatase-dependent and -independent mechanisms. HSCs, hematopoietic stem cells; HSPCs, hematopoietic stem and progenitor cells; MCL-1, myeloid cell leukemia-1; SALL4, spalt like transcription factor.

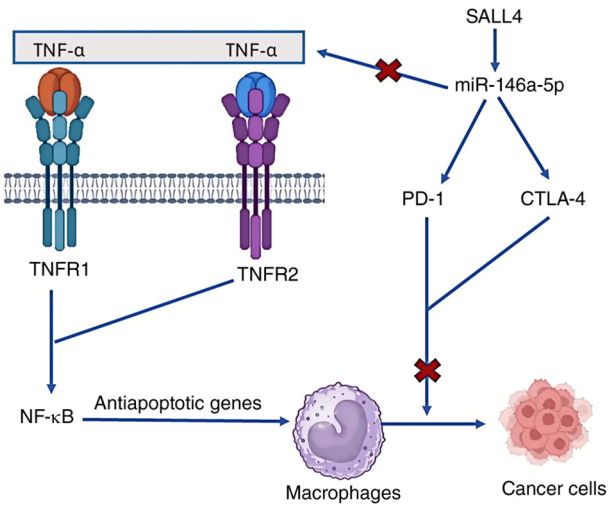


Figure 3. SALL4 promotes the expression of miR-146a-5p decreasing the antitumor effect of macrophages. TNF activates the NF-κB pathway, protecting monocytes and macrophages from apoptosis. Monocytes and macrophages resist tumors; SALL4 promotes the expression of miR-146a-5p inhibiting the expression of TNF-α and upregulating the expression of inhibitory receptors such as programmed PD-1 and CTLA-4. CTLA-4, cytotoxic T-lymphocyte-associated protein 4; miR, microRNA; PD-1, programmed death ligand 1; SALL4, spalt like transcription factor; TNFR, TNF receptor.

contributes to immune suppression by directly binding to the promoter of miR-146a-5p and promoting its transcription, thereby attenuating the immune effector functions of macrophages. In addition, SALL4 can further modulate miR-146a-5p

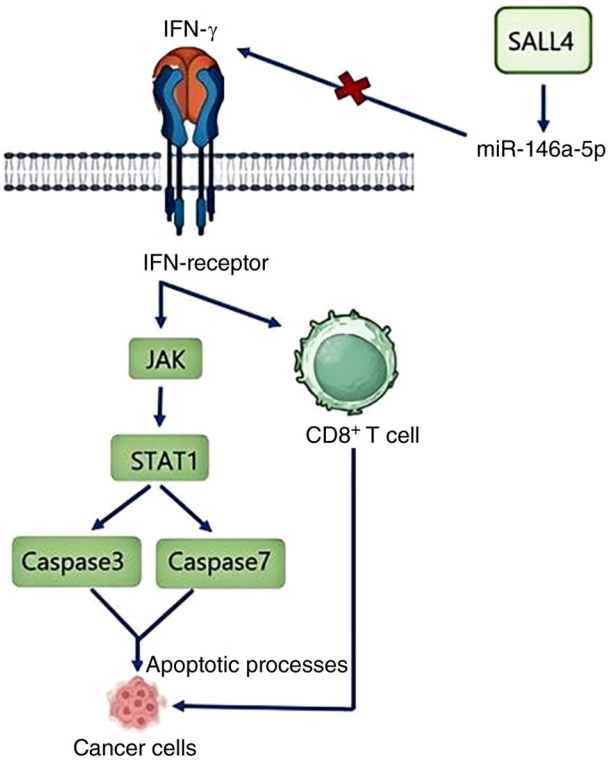


Figure 4. SALL4 inhibits IFN-γ by binding to miR-146a-5p. IFN-γ activates JAK-STAT1-caspase 3/caspase 7 initiating apoptotic processes in cancer cells; IFN-γ increases the motility of antigen-specific $CD8^+$ T cells to the antigen expressing (target) cells and enhances the killing capacity of target cells. JAK, Janus kinase; miR, microRNA; SALL4, spalt like transcription factor; IFN, interferon.

activity to induce T-cell exhaustion, ultimately impairing systemic adaptive antitumor immunity (52).

IFN-γ. IFN-γ is the sole member of the type II IFN family. In human blood, IFN-γ exists in three distinct molecular weight fractions (53). This cytokine exhibits pro-apoptotic activity against tumor cells by activating the Janus kinase (JAK)-STAT1 signaling pathway, which subsequently triggers caspase-dependent apoptosis. STAT1 promotes the transcriptional activation and subsequent expression of caspase-3 and caspase-7, thereby triggering apoptosis in malignant cells (54). IFN-γ enhances the migratory capacity of antigen-specific $CD8^+$ T lymphocytes toward target cells expressing cognate antigens, while simultaneously augmenting their cytotoxic activity against these cells (55). IFN-γ is recognized as a pivotal regulator of immunotherapy efficacy, particularly for immune checkpoint blockade targeting PD-1, programmed death-ligand 1 (PD-L1) and CTLA-4 pathways (56). In hepatocellular carcinoma and hematological malignancies, SALL4 inhibits IFN-γ by binding to miR-146a-5p preceding part of the text like TNF-α (51,52). The underlying mechanisms are summarized in Fig. 4.

Apoptosis-inhibiting genes

Bmi-1. Bmi-1 belongs to the Polycomb group protein family, originally characterized in *Drosophila melanogaster* for its role in transcriptional repression of homeobox genes (57). In humans, Bmi-1 serves as a critical regulator of HSC self-renewal in adult tissues and contributes to the maintenance of leukemic

stem cell (LSC) populations (58). Bmi-1 demonstrates high expression levels in HSCs that progressively decrease during cellular differentiation. Clinically, Bmi-1 expression patterns serve as a valuable prognostic indicator for both MDS progression and its transformation to AML (59). SALL4 positively and directly regulates Bmi-1 by binding to the Bmi-1 promoter, and the SALL4 responsiveness of the Bmi-1 promoter exhibits dose-dependent activation (60). Notably, SALL4 upregulation is associated with enhanced histone H3 lysine 4 (H3K4) and lysine 79 (H3K79) methylation marks within the Bmi-1 promoter region. SALL4 subsequently silences p16INK4a and p19ARF, abrogating the p53-mediated apoptotic pathway and sustaining the self-renewal capacity of LSCs (61). The SALL4/Bmi-1 network, through their cooperative effects, plays an important role in leukemogenesis.

BCL-2. The BCL-2 family represents a crucial class of apoptosis-regulating proteins that primarily modulate the mitochondrial pathway of programmed cell death (62). The BCL-2 protein family consists of three functionally distinct subgroups: i) Pro-apoptotic BCL-2 homology 3 (BH3)-only proteins; ii) anti-apoptotic proteins; and iii) pro-apoptotic effector proteins. Apoptotic signaling is triggered when anti-apoptotic BCL-2 family members are inhibited through either BH3-only protein binding or proteolytic degradation. Under physiological conditions, a delicate equilibrium exists between pro-death BH3-only proteins and pro-survival BCL-2 family members to maintain cellular homeostasis (63). Anti-apoptotic BCL-2 family proteins suppress intrinsic apoptosis by sequestering pro-apoptotic effectors BAX and BAK, thereby preventing caspase activation. This molecular mechanism underlies the pathogenesis of human follicular lymphoma, where dysregulated BCL-2 activity promotes malignant cell survival (64). The anti-apoptotic proteins BCL-XL and MCL-1 represent critical members of the BCL-2 family. Overexpression of BCL-2 confers multidrug resistance in both malignant and normal cell populations by potently inhibiting apoptotic pathways (65). Notably, the therapeutic efficacy of BCL-2-targeted inhibition is tightly modulated by p53 status in AML cells. Concurrently, activated p53 exerts dual pro-apoptotic effects by suppressing the Ras/Raf/MEK/ERK signaling cascade and activating GSK-3β to promote MCL-1 phosphorylation and subsequent proteasomal degradation. Collectively, this p53-dependent signaling disruption impairs anti-apoptotic networks and sensitizes AML cells to BCL-2-targeted therapies (43). Wang *et al* (66) found that in myeloid neoplasms cells, the oncogenic transcription factor SALL4 directly upregulates BCL-2 expression, thereby enhancing cellular survival pathways. In MDS and AML, elevated SALL4 levels are associated with increased BCL-2 expression, which confers a pro-survival advantage to malignant cells.

Cell cycle-related genes

c-Myc. The transcription factor c-Myc plays a crucial role in regulating cell proliferation, differentiation and programmed cell death. Dysregulation of c-Myc expression is strongly linked to tumorigenesis, with its upregulation observed in a wide range of human malignancies, such as hematopoietic cancer, sarcomas and carcinomas derived from epithelial tissues (67). The c-Myc-encoded protein functions as a key transcriptional regulator, orchestrating diverse cellular processes by modulating the expression of numerous target genes, either directly through DNA binding or indirectly via downstream signaling networks (68). Myc protein also regulates host immunity and the tumor microenvironment (69). Myc modulates antitumor immunity by transcriptionally controlling key immune checkpoint molecules such as PD-L1 and CD47. Experimental evidence from hematopoietic malignancy models demonstrates that Myc directly binds to the CD274 gene promoter (encoding PD-L1) to drive its expression (70). In hematological malignancies, upregulated c-Myc is found in Burkitt lymphoma, diffuse large B-cell lymphoma, multiple myeloma and chronic lymphocytic leukemia (71). Bmi-1 synergizes with c-Myc to promote retrovirus-mediated leukemogenesis in both B and T lymphocytes (72). In human choriocarcinoma cells, SALL4 upregulates c-Myc expression and enhances cellular proliferation. Mechanistically, SALL4 facilitates nuclear translocation of β-catenin, a known upstream regulator of c-Myc. However, β-catenin knockdown experiments revealed that SALL4-mediated c-Myc activation and proliferative effects were only partially attenuated, suggesting the existence of additional β-catenin-independent regulatory pathways (73). In addition to canonical Wnt/β-catenin signaling, SALL4 may directly bind to the c-Myc promoter or modulate c-Myc stability through epigenetic regulators such as the NuRD complex, HDACs or PTEN/PI3K/AKT signaling. SALL4 has been shown to epigenetically remodel chromatin and recruit transcription cofactors independently of β-catenin, which could sustain c-Myc expression and drive cell cycle progression, even in the absence of intact β-catenin activity (38,52). These observations imply that SALL4 functions as a central upstream hub capable of orchestrating c-Myc-driven oncogenic programs through multiple parallel pathways, further highlighting its value as a critical therapeutic target in hematological malignancies.

Cyclin D. Cyclin D1, a key G1-phase regulator and Wnt signaling target, critically drives cell cycle progression and oncogenesis. As a pivotal G1 cyclin, it facilitates the G1/S transition, and its aberrant upregulation is strongly associated with malignant transformation. The oncogenic potential of Cyclin D1 stems not only from its central cell cycle function but also from its position as a downstream effector of the Wnt pathway, making it a molecular linchpin in human cancer development (74,75). In solid tumors, SALL4 primarily modulates cell proliferation, invasion and metastasis through its interaction with Cyclin D1, without directly regulating cancer stem cell stemness, and is involved in relatively few synergistic signaling pathways (76). By contrast, in hematological malignancies, the SALL4-Cyclin D1 axis plays a central role in governing LSC stemness, G1/S checkpoint dysregulation and chemoresistance, and acts in strong synergy with the SALL4-Bmi-1 and SALL4-p53 pathways (52). In cervical cancer cells, SALL4 potently activates the Wnt/β-catenin signaling cascade, leading to the transcriptional upregulation of key oncogenic targets such as c-Myc and Cyclin D1 (77). In liver cancer cells, SALL4A upregulation induces Cyclin D1 and Cyclin D2, controlling G1-S transition and regulating cell proliferation (78). Notably, research has demonstrated that Ras-Cyclin D2 activation plays a pivotal role in driving both tumorigenesis and self-renewal processes in spermatogonial

stem cells (79). In AML cell proliferation, $CD34^+CD38^-$ LSCs characterized by high SALL4 and Cyclin D1 expression, display stronger self-renewal potential and increased resistance to chemotherapy (80).

Transcription factor

HOXA9. HOX genes encode critical transcription factors that orchestrate fundamental biological processes by modulating key signaling molecules essential for physiological homeostasis and tissue maintenance (81). Maladaptive HOXA9 expression drives tumor progression through dual mechanisms of immune evasion and persistent pro-growth signaling pathway activation (82). HOXA9 has been extensively studied, particularly in the context of hematological malignancies, and is the crucial regulator of hematopoiesis (83). In the hematopoietic hierarchy, HOXA9 expression is tightly regulated; abundant in primitive HSPCs but sharply attenuated upon lineage commitment (84). HOXA9 upregulation promotes myeloid lineage commitment by activating the NF-κB signaling cascade, as demonstrated by increased expression of downstream targets (85). AML patient cohorts exhibit a spectrum of HOXA9 alterations, including both genetic mutations and epigenetic dysregulation, which functionally contribute to malignant transformation (86). In leukemogenesis, HOXA9 orchestrates a critical oncogenic network by directly regulating BCL2 expression, which mediates hematopoietic cell immortalization and myeloid progenitor survival. Concurrently, HOXA9 modulates PTEN expression, thereby dysregulating PI3K signaling to promote proliferation and suppress apoptosis (82). In hematopoietic cells, SALL4 occupies the HOXA9 promoter and maintains elevated H3K4me3 and H3K79me3 histone modifications at this locus, thereby upregulating HOXA9 expression and modulating its downstream molecular events (87). Experimental data revealed marked HOXA9 upregulation in SALL4B-driven leukemic cells relative to wild-type controls. Genetic suppression of HOXA9 in these cells impaired proliferative capacity *in vitro* and notably delayed AML progression in murine xenograft models, a phenotype recapitulated in human AML cells. These results established the SALL4/HOXA9 axis as a conserved mechanistic pathway driving myeloid leukemogenesis across species (33,87).

3. Role of SALL4 in hematological malignancies

SALL4 is an important stemness transcription factor in HSCs and its upregulation relates to downstream genes regulating hematological malignancies. SALL4 plays critical roles in both cell proliferation and clinical prognosis, particularly in AML, acute lymphoblastic leukemia (ALL), MDS, chronic myeloid leukemia (CML) and mixed lineage leukemia rearranged leukemogenesis (MLL-r).

AML. In normal hematopoietic cells, SALL4 is highly expressed in $CD34^+$ HSPCs and HSCs, and it is undetectable in $CD34^-$ cells. Constitutive expression of SALL4 transgene is a key inducement of AML development in mice (88). SALL4 expression has been documented not only in mouse models but also in most AML subtypes, where it accelerates disease progression and contributes to a poor prognosis (89). Multiple key molecules, including PTEN, Bmi-1, BCL-2 and HOXA9, have been demonstrated to be directly associated with SALL4-mediated leukemogenesis in AML (33,59,66). HOXA9 serves as a critical survival determinant in human leukemia subtypes harboring MLL translocations. Mechanistically, SALL4 regulates HOXA9 expression in AML cells via direct binding to the HOXA9 promoter in complex with MLL proteins. This SALL4/MLL-mediated transcriptional activation of HOXA9 establishes the SALL4-HOXA9 axis as a fundamental driver of AML pathogenesis (87). SALL4 can also impair DNA-damage repair processes, thereby accelerating AML progression (66). Emerging evidence suggests a feedforward regulatory loop in AML pathogenesis where Wnt/β-catenin signaling activates SALL4 expression, which in turn amplifies Wnt pathway activity through transcriptional regulation. This SALL4-Wnt/β-catenin axis creates a self-reinforcing oncogenic circuit that drives and maintains AML progression (10). DNA methylation functions as a key epigenetic silencing mechanism, predominantly occurring at CpG islands in gene promoter regions to suppress transcription. In AML, SALL4 promoter hypomethylation at these regulatory CpG sites is associated with its aberrant upregulation, suggesting epigenetic dysregulation as a driver of leukemogenesis (90). SALL4 serves as both a treatment response biomarker and therapeutic target in AML, with expression levels inversely associated with remission status. Functionally, SALL4 upregulation confers pro-leukemic properties, including therapy-resistant proliferation, explaining its association with adverse prognosis (88). Wang *et al* (61) found that SALL4 expression levels declined during the treatment process in the drug responsive group and increased in the drug resistant group. SALL4 regulates the expression of HOXA9 and Ki-67, which are related to poor proliferation (83,91). In the treatment of AML type M3, SALL4 upregulation notably impairs all-trans retinoic acid-induced myeloid differentiation and apoptosis, as demonstrated by reduced CD11b/CD14 expression and diminished caspase activation in treated leukemic blasts (5). Through transcriptional upregulation of HOXA9 and BCL-2 as aforementioned, SALL4 also promotes therapeutic drug resistance in AML (92). Within the 2022 European LeukemiaNet risk-stratification system, patients with intermediate-risk karyotype accompanied by high SALL4 expression, can be reclassified into the high-risk group, warranting intensive induction chemotherapy followed by allogeneic HSC transplantation (5). Furthermore, persistently high SALL4 expression indicates positive minimal residual disease and confers a markedly elevated risk of disease relapse (93,94).

ALL. Transcriptomic analyses demonstrate that three of four B-cell ALL (B-ALL) cases exhibit aberrantly elevated SALL4 expression, implicating this oncogene in B-ALL leukemogenesis (13). SALL4 serves as a prognostic biomarker in pediatric B-ALL, with its upregulation defining a distinct subgroup of high-risk patients who demonstrate poorer treatment responses and reduced survival outcomes (95). Epigenetic profiling reveals that promoter hypomethylation of CpG islands contributes to aberrant SALL4 upregulation in B-ALL, representing a key regulatory mechanism in leukemogenesis (12). SALL4 can also regulate early B-cell factor 1, a master transcription factor essential for B-cell lineage differentiation (96). As an

apoptosis-inhibiting gene, Bmi-1 is upregulated in ALL, which is associated with a poor prognosis response to prednisone and a higher clinical risk of ALL. Therefore SALL4 can act on Bmi-1, influencing the prognosis of ALL (97). Emerging evidence indicates that SALL4 can directly bind to the promoter regions of ATP-binding cassette (ABC) transporter genes, ABCA2 and ABCA3 (10). These transporters have been demonstrated to play significant prognostic roles in mediating drug resistance in pediatric ALL, as well as contributing to multidrug resistance (MDR) in various human malignancies (98). Notably, MDR represents a primary factor leading to chemotherapy failure and subsequent disease recurrence in cancer treatment. SALL4 exhibits markedly low expression in T-ALL (13). By contrast, high SALL4 expression in B-ALL is associated with poor prognosis, increased relapse rate and notably shortened disease-free survival and overall survival (OS) (99). Consequently, SALL4 has emerged as a potential biomarker for predicting treatment resistance and relapse risk in childhood ALL cases (100).

MDS. SALL4 is upregulated in patients newly diagnosed with MDS, especially in those who have high grade International Prognostic Scoring System scores (61). SALL4 shows markedly higher expression in patients diagnosed with refractory anemia with excess blasts-1 (RAEB-1) and its advanced stage, RAEB-2. This differential expression profile suggests SALL4 may serve as a potential molecular marker for disease progression in MDS, particularly in cases exhibiting increased blast counts (61). The heightened expression levels observed in these high-risk MDS subtypes are associated with more aggressive disease phenotypes and poorer clinical outcomes, highlighting its potential prognostic significance in hematological malignancies (61). Among high-risk MDS patients, 30-40% will progress to secondary AML, and these transformed cases are more difficult to treat than *de novo* AML (98). These patients with MDS-derived AML (MDS-AML) have poor prognosis and a short survival time (101). In the process of MDS transformation to AML, SALL4 expression increases markedly. Regarding other related genes, Wang *et al* (61) found elevated co-expression of Bmi-1 and SALL4 in $CD34^+$ hematopoietic progenitor cells across various high-risk MDS subtypes, including RAEB, RAEB in transformation (RAEB-t) and MDS-AML. This consistent upregulation pattern suggests that both SALL4 and Bmi-1 may serve as valuable biomarkers for prognostic evaluation in MDS progression. Shuai *et al* (72) also found that SALL4 upregulated downstream genes Myc and Cyclin D1 through activating the Wnt/β-catenin pathway, participating in MDS pathogenesis.

CML. The oncogenic transcription factor SALL4 plays a critical role in sustaining CML cell proliferation and survival, with its expression levels associated with disease progression to advanced stages (102). An experimental study has demonstrated that SALL4 knockdown induces cell cycle arrest and promotes apoptosis in CML cells, suggesting its potential as a therapeutic target for CML treatment (102). The expression of SALL4 exhibits phase-dependent variation in CML, with markedly elevated levels observed in the blast crisis (BC) phase compared with both the chronic phase (CP) and complete remission (CR) phase. In patients with CML in the BC phase, 75% exhibit high SALL4 expression, serving as an independent adverse prognostic factor, with a median OS time of <6 months (103). Notably, Bmi-1 displays a similar expression pattern across CML disease stages. Furthermore, SALL4 expression in the CP phase is markedly lower than in the CR phase, suggesting its potential role in disease progression and therapeutic response (104). A study by Cui *et al* (13) involving comparative analyses revealed notably elevated SALL4 expression levels in precursor B-ALL and AML when compared with healthy individuals. These differential expression patterns suggest distinct biological functions and leukemogenic mechanisms of SALL4 in AML vs. CML, highlighting its disease-specific roles in leukemogenesis. To test whether SALL4B overexpression could cooperate with breakpoint cluster region-Abelson murine leukemia viral oncogene (BCR-ABL) in CML, Lu *et al* (102) found that *BCR-ABL*-transduced SALL4B leukemic cells were more immature and less differentiated. In the treatment of CML, BCR-ABL1 tyrosine kinase inhibitors (TKIs) reliably induced disease remission for patients with CML (105). However, experimental evidence indicates that ABCA3 transporter activity confers protection to leukemic cells against TKI-induced cytotoxicity, including therapeutic agents such as imatinib, dasatinib and nilotinib. This protective mechanism contributes to the development of TKI resistance in leukemia treatment. One mechanistic study revealed that SALL4 transcriptionally activates ABCA3 expression through direct promoter binding, establishing a self-reinforcing protective mechanism in leukemic stem cells (106). This SALL4-ABCA3 autoregulatory axis persists during TKI therapy, maintaining drug resistance in residual leukemic cell populations, despite successful eradication of the bulk leukemia mass. Notably, this molecular cooperation contributes markedly to the development of TKI resistance in CML (107).

MLL-r. The MLL gene, located at chromosome 11q23, encodes a critical epigenetic regulator and represents one of the most significant driver mutations in acute leukemias. Clinically, MLL (also termed KMT2A) rearrangements account for 70-80% of infant ALL and 35-50% of AML cases in children under 1 year of age (global pooled estimates) (108). These translocations constitute an independent, high-risk prognostic marker associated with poor clinical outcomes in patients with pediatric acute leukemia (109). These infant patients with ALL and wild-type MLL have a 5-year event free survival (EFS) rate of 60%, but those who MLL rearrangement have only a 35% 5-year EFS rate (110). Most partner genes are MLL-1 fused gene from chromosome 4 (AF4), AF6, AF9, AF10, eleven-nineteen leukemia and eleven-nineteen lysine-rich leukemia (111). HOXA9 and SALL4 function as key oncogenes essential for the survival of MLL-r leukemia cells. Notably, HOXA9 dysregulation serves as a dominant driver in MLL-r leukemogenesis. Mechanistically, HOXA9 directly regulates the distal enhancer (h-FLT3) of FLT3, inducing its high expression, a hallmark feature of MLL-r ALL that contributes to its distinct molecular identity (112).

SALL4 has emerged as a promising therapeutic target in MLL-AF9 leukemia due to its critical role in maintaining leukemogenic programs. Mechanistically, SALL4 recruits chromatin-modifying enzymes, including the histone

demethylase lysine-specific demethylase 1 and the H3K79 methyltransferase disruptor of telomeric silencing 1-like, to enforce the MLL-AF9 oncogenic transcriptional network. In MLL-r, high SALL4 expression is directly associated with marked chemoresistance, early relapse and poor prognosis. Such cases are stratified into the high-risk group, with a cure rate of <20% using conventional chemotherapy (113). Targeting this epigenetic axis may provide a novel strategy to disrupt leukemia maintenance (114). In addition to AML, MDS, ALL, MLL-r and CML, SALL4 expression is rarely detected in most other hematological malignancies, such as Hodgkin and non-Hodgkin lymphomas, multiple myeloma and chronic lymphocytic leukemia (13).

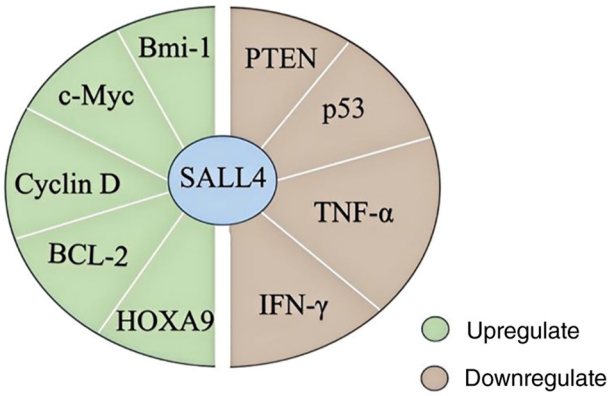


Figure 5. Regulatory effects of SALL4 on its downstream targets. SALL4 downregulates apoptosis-inducing genes (PTEN and p53) and inflammatory factors (TNF-α and IFN-γ), upregulates apoptosis-inhibiting genes (Bmi-1 and BCL-2), cell cycle-related genes (c-Myc and Cyclin D) and transcription factor HOXA9. Bmi-1, B cell-specific moloney murine leukemia virus integration site 1; SALL4, spalt like transcription factor; IFN, interferon.

4. Challenges and future perspectives

As a transcription factor, SALL4 is expressed in several malignant hematological neoplasms and represents an emerging therapeutic target. However, its clinical translation remains limited due to several inherent targeting challenges. The core limitations mainly lie in four aspects: i) Poor druggability of the target; ii) subtype and expression heterogeneity; iii) off-target effects and drug resistance; and iv) complexity of regulatory mechanisms. As a nuclear ZF transcription factor, SALL4 lacks a typical active pocket accessible to small molecules, making it difficult for conventional small molecule inhibitors to directly block its function (99). Furthermore, SALL4 exerts its oncogenic effects through interactions with epigenetic complexes such as NuRD and HDAC, rather than through a single enzymatic active site, which further complicates rational drug design (38). SALL4 exhibits a heterogeneous expression profile in hematological malignancies, with aberrant upregulation restricted to subsets of AML, MDS and other high-risk blood cancer types. In patients with AML, 30-55% are SALL4-positive, and targeted therapy shows little to no efficacy in SALL4-negative cases (99). Moreover, the druggability varies considerably across SALL4 isoforms. For instance, immunomodulatory imide drugs (IMiDs) selectively degrade the SALL4A isoform but spare SALL4B (103). Given that SALL4B is essential for the survival of LSCs, single targeting of SALL4A may lead to compensatory drug resistance driven by the remaining SALL4B isoform (115). SALL4 is also expressed at low levels in normal $CD34^+$ HSPCs. Targeted inhibition may therefore damage normal hematopoiesis, causing severe myelosuppression, pancytopenia and other dose-limiting toxicities. Targeting SALL4 can eliminate the majority of bulk leukemia cells but fails to eradicate quiescent LSCs. Persistent residual LSCs can rapidly reconstitute drug resistant clones and drive disease relapse via upregulation of stemness maintaining pathways, including Bmi-1 and Wnt/β-catenin (116). Moreover, hematological malignancies are driven by multiple oncogenic signaling cascades; monotherapy targeting SALL4 alone cannot block all oncogenic signals, thus failing to achieve deep and durable therapeutic remission (52).

To address the challenges of poor druggability and isoform heterogeneity of SALL4, researchers have targeted the fourth ZF cluster (ZFC4), a non-IMiD structural domain of SALL4. Combining the ZFC4-DNA crystal structure, computational docking simulations and cell viability assays, multiple compound libraries have been screened against a putative druggable binding pocket, leading to the identification of SH6, a small molecule that selectively targets SALL4-expressing cancer cells. SH6 treatment markedly inhibits tumor growth by 87% in SALL4-positive patient-derived xenografts, and pharmacokinetic studies confirmed its favorable bioavailability (117). To overcome the inefficiency of monotherapy and drug resistance-induced relapse, SALL4 inhibitors can be used in combination with other agents, including inhibitors of Bmi-1 and the Wnt/β-catenin pathway, HDAC inhibitors and hypomethylating agents (99,118). These findings provide novel insights for further exploring SALL4 as a therapeutic target. The development of new small molecule targeted agents and more diversified combination regimens represent promising directions for future research.

5. Conclusions

As a key transcription factor, SALL4 modulates a wide range of downstream targets to exert oncogenic roles; it represses pro-apoptotic genes including PTEN and p53 as well as inflammatory cytokines such as TNF-α and IFN-γ, while upregulating anti-apoptotic genes (Bmi-1 and BCL-2), cell cycle regulators (c-Myc and Cyclin D) and the stemness transcription factor, HOXA9. These events collectively promote tumor cell proliferation, drive disease progression and lead to poor prognosis and drug resistance. The effects of SALL4 on downstream genes and proteins are summarized in Fig. 5.

The present review focused on the role of SALL4 in hematological malignancies. SALL4 is aberrantly upregulated in AML, ALL, CML, MDS and MLL-r leukemia, where it accelerates disease progression and is associated with unfavorable outcomes and therapeutic resistance. In CML, SALL4 expression varies dynamically across disease phases, supporting its value as a biomarker for staging. Reducing or inhibiting SALL4 in the CP may delay or even prevent progression to blast crisis. Similarly, high SALL4 expression is detected in high-risk MDS subtypes (RAEB and RAEB-t) and MDS-derived AML, suggesting its involvement in

malignant transformation. Inhibiting SALL4 expression or disrupting its downstream signaling represents a novel and effective therapeutic approach. Notably, *in vivo* knockout studies indicate that SALL4 depletion has minimal impact on normal hematopoiesis, highlighting the safety and potential of SALL4-targeted therapy for hematologic malignancies (114). However, several mechanistic insights remain derived primarily from solid tumors, such as liver cancer, and studies in spermatogonia (119). Further in-depth investigations are warranted to fully clarify the specific functions and precise molecular mechanisms of SALL4 in hematological malignancies and to validate its clinical utility as a therapeutic target.

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Authors' contributions

QW wrote the original draft, WL and YL contributed to editing the manuscript, and TW contributed to the writing, reviewing and editing the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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