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Review Article

Roles of Krüppel-like factor 6 splice variant 1 in the development, diagnosis, and possible treatment strategies for non-small cell lung cancer

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Abstract: Krüppel-like factor 6 (KLF6) is a nuclear transcriptional regulator found in mammalian tissue that has been identified as a tumor suppressor gene in several malignancies. As a result of loss of heterozygosity, DNA methylation, and alternative splicing, it is frequently inactivated in various malignancies. Krüppel-like factor 6 splice variant 1 (KLF6-SV1), Krüppel-like factor 6 splice variant 2, and Krüppel-like factor 6 splice variant 3 alternatively spliced isoforms that emerge from a single nucleotide polymorphism in the KLF6 gene. KLF6-SV1 is generally up-regulated in multiple cancers, and its biological function is well understood. Overexpression of KLF6-SV1 inhibits the KLF6 gene function while promoting tumor progression, which is associated with a poor prognosis in patients with various malignancies. We reviewed the progress of KLF6-SV1 research in NSCLC over the last several years to understand the molecular mechanisms of tumorigenesis, tumor development, and therapy resistance. Finally, this review emphasizes the therapeutic potential of small interfering RNA targeted silencing of KLF6-SV1 as a novel strategy for managing chemotherapy resistance in NSCLC patients.

Keywords: KLF6-SV1, NSCLC, proliferation, EMT, siRNA, chemotherapy resistance

Introduction

Lung cancer has a high morbidity and mortality rate in the world. Non-small cell lung cancer (NSCLC) accounts for more than 85% of lung cancers, with squamous cell carcinomas and adenocarcinomas being the most common types [1]. Surgery is still the primary clinical treatment option for early-stage NSCLC [2]. However, more than 70% of NSCLC patients are identified at the initial visit in the intermediate or late stages [3]. Even when various clinical treatment strategies, such as surgery, radiotherapy, and chemotherapy [4], are used, the therapeutic effect is still unsatisfactory [5, 6]. Despite the discovery of numerous tumor suppressor genes and oncogenes in related research, the key cause of NSCLC remains unknown [7]. As a result, molecular mechanisms involved in NSCLC and the identification of potential molecular markers for targeted therapy are crucial for early diagnosis and treatment. In recent studies, the Krüppel-like factor 6 (KLF6) gene functional inactivation and high expression levels of Krüppel-like factor 6 splice variant 1 (KLF6-SV1) have been linked to NSCLC progression and poor prognosis. This article summarizes the functions and molecular mechanisms of KLF6-SV1 in cell proliferation, invasion, and metastasis, hoping to provide new research directions for NSCLC therapy.

The KLF6 gene

In the 1990s, researchers detected the KLF6 gene in placental cells [8], hepatic stellate cells [9], and peripheral blood lymphocytes of patients with chronic lymphoblastic leukemia [10]. KLF6 is a ubiquitous nuclear transcriptional regulator found in many mammalian organs that belongs to the Krüppel-like factor family. KLF6 has a total length of 7 kb and is found on human chromosome 10 (10p15) [11]. Three domains comprise the KLF6 protein (**Figure 1**) [12-15]. The acidic domain at the amino terminus of proline and serine is important in tran-

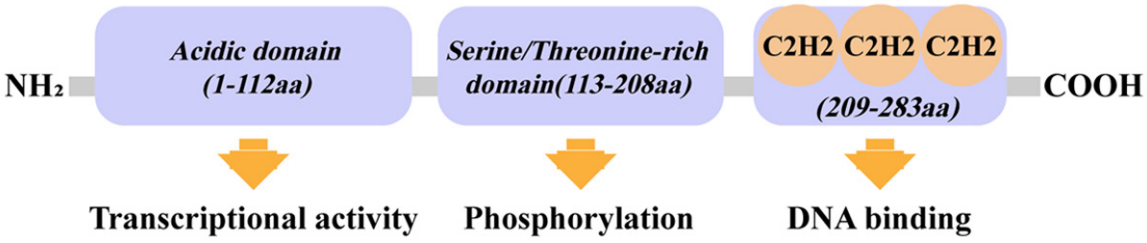

Figure 1. KLF6 protein structure and the associated post-translational modifications. The KLF6 protein consists of three domains: the N-terminal acidic domain, Serine/Threonine-rich central domain, and the C-terminal DNA-binding domain.

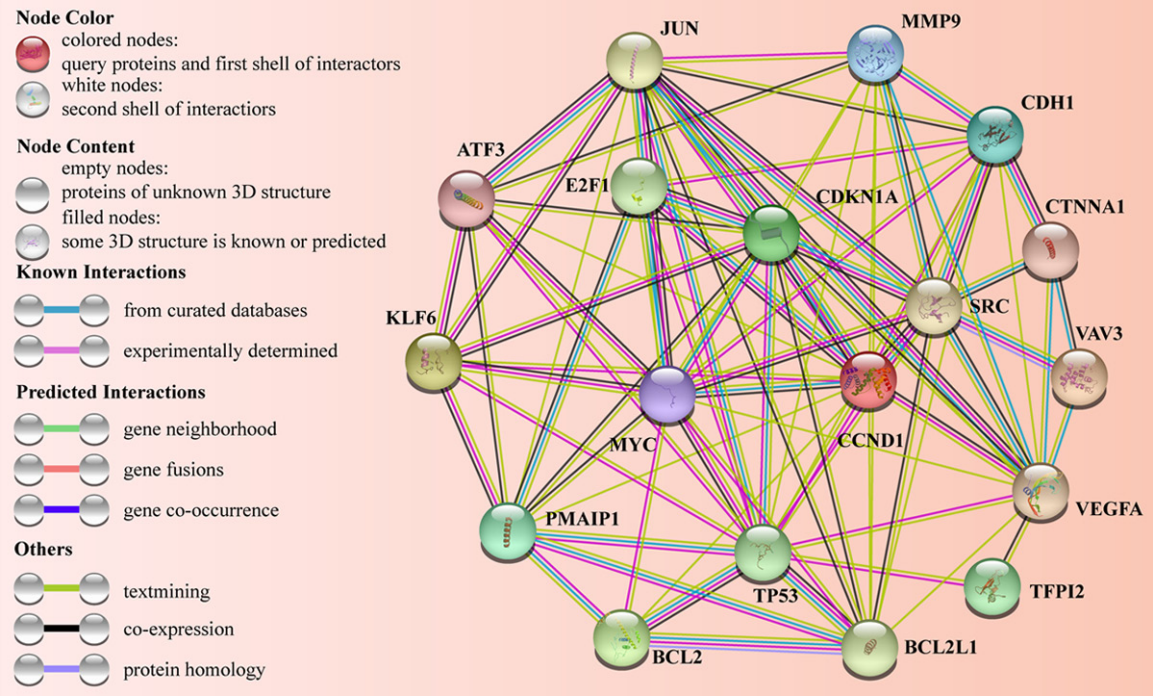

Figure 2. KLF6 interacts with key genes in many cancer-related signaling pathways. Protein-protein interaction data were obtained from the STRING database (https://cn.string-db.org/).

scriptional activity [16]. The serine/threonine-rich intermediate region of the KLF6 protein is involved in transcriptional and post-translational regulation mechanisms [17]. Like other Krüppel-like factor family genes, the hydroxyl terminus has a conserved DNA binding domain composed of three Cys2-His2 zinc finger structures that recognize and bind to the GC box and CACCC promoter elements in the target gene promoter [8, 18].

Roles of KLF6 in tumorigenesis and development

The anticancer function of KLF6 was initially discovered in prostate cancer [19]. KLF6 was later identified as a tumor suppressor gene in glioma [20], ovarian cancer [21], and liver cancer [22] and linked to gene interactions. In the STRING database, KLF6 interacted with key genes in many cancer-related signaling pathways (**Figure 2**). KLF6 can upregulate $p21^{WAF1/CIP1}$ (19) without p53 and then inhibit the activity of the cyclinD1/CDK4 complex, resulting in cell cycle G1 arrest and growth retardation [23]. Furthermore, KLF6 has several downstream target genes, including pregnancy-specific glycoproteins [24], transforming growth factor-β1 [25], transforming growth factor-β receptors [26], and others [27-40]. KLF6 is also involved in many tumor-related signaling pathways, including inducing apoptosis

[27], inhibiting the activity of the c-Jun proto-oncoprotein [28], decreasing E-cadherin expression [21], transactivating the c-MYC gene (29), and lowering vascular endothelial growth factor expression [30].

Functional inactivation of KLF6 in tumors

As tumor pathogenesis research has advanced in recent years, more evidence has emerged that functional inactivation of KLF6 plays a nuanced and essential role in malignancies. In most cancers, KLF6 is functionally inactivated as a tumor suppressor gene. Point mutations, DNA methylation, loss of heterozygosity (LOH), and alternative splicing (AS) are the primary causes of KLF6 functional inactivation.

KLF6 is thought to contribute to prostate cancer because it is located on chromosome 10p15, and prostate cancer frequently exhibits LOH in this region [41]. Narla et al. confirmed that more than 70% of the KLF6 alleles were mutated after genetic testing of prostate tissue [19]. For the first time, the LOH of the KLF6 gene was found to be involved in carcinogenesis and development [42]. Since then, deletion or mutation of KLF6 has been identified in tumors such as NSCLC [27], colorectal cancer [43], liver cancer [22, 44, 45], gastric cancer [46], and astrocytoma [47, 48]. The LOH level of the KLF6 gene in ovarian and gastric cancer is strongly linked to tumor stage and grade, and the detection rate of LOH in advanced cancer is much higher than in earlier stages [30, 49]. The deletion of the KLF6 allele is closely linked to recurrence and survival in the head and neck squamous cell carcinomas. KLF6 is regarded as an excellent prognostic indicator [50]. Hypermethylation of CpG islands in the promoter region is one of the most common manifestations of aberrant methylation of tumor suppressor genes, which is one of the most critical causes of carcinogenesis [51, 52]. Hypermethylation of CpG islands in promoter regions can alter the cell cycle, DNA repair, tumor metabolism, tumor angiogenesis, apoptosis, and cell-cell interactions, all of which are strongly associated with tumorigeneses [53, 54]. Song et al. [55] found that methylated DNA appears in liver cancer tissues, and patients with KLF6 gene methylation have a history of hepatitis B virus (HBV) infection or liver cirrhosis. If the KLF6 gene is methylated abnormally, HBV infection or liver cirrhosis can transform into liver cancer. DNA methylation of the KLF6 gene is also observed in esophageal cancer, which is closely linked to malignant tumor progression [56].

We discovered that AS of the KLF6 gene is frequent in a range of malignancies, in addition to the pathways mentioned above. A single nucleotide polymorphism (SNP) can cause aberrant gene splicing, and roughly 15% of genetic variants in hereditary disorders influence precursor messenger RNA (pre-mRNA) splicing.

The process of KLF6-alternative splicing to generate KLF6-SV1

SNP can increase the AS of the KLF6 gene. KLF6-SV1, Krüppel-like factor 6 splice variant 2 (KLF6-SV2), and Krüppel-like factor 6 splice variant 3 (KLF6-SV3) are three splice variants caused by a SNP (**Figure 3**) [57]. KLF6-SV1 is considered to be an oncogene involved in the malignant development of many tumors. KLF6-SV2 acts as an antiproliferative and pro-apoptotic factor in colorectal and liver cancers. The function of KLF6-SV3 is unknown (**Table 1**). Overexpression of KLF6-SV1 reduces the tumor suppressor activity of KLF6 and is linked to various human cancers [79, 80], including prostate cancer [57-59], lung cancer [60, 62-66], ovarian cancer [30, 61], hepatocellular carcinoma (HCC) [71, 72], and pancreatic cancer [74].

AS modification affects more than 90% of human genes, which is the primary cause of protein variation [81]. Exons of a single gene's pre-mRNAs are spliced and modified in various ways, resulting in mRNA and protein variants with different structures and functions [82]. These modifications play critical roles in multiple biological processes [83, 84].

AS dysregulation is caused by several physiological and pathological mechanisms, including disruption of critical tumor-associated cellular signaling [85, 86]. When tumor cells produce AS, they can silence tumor suppressor genes and activate oncogenes [87]. These AS events promote tumor cell proliferation, invasion, metastasis, drug resistance, and immune evasion [88]. AS of the KLF6 gene is a typical example. Intron 1 of the KLF6 gene is prone to point mutations, which contribute to the formation of the SR protein's binding site (SRp40). The SRp40 novel site is considered an atypical intronic splicing enhancer, activating three

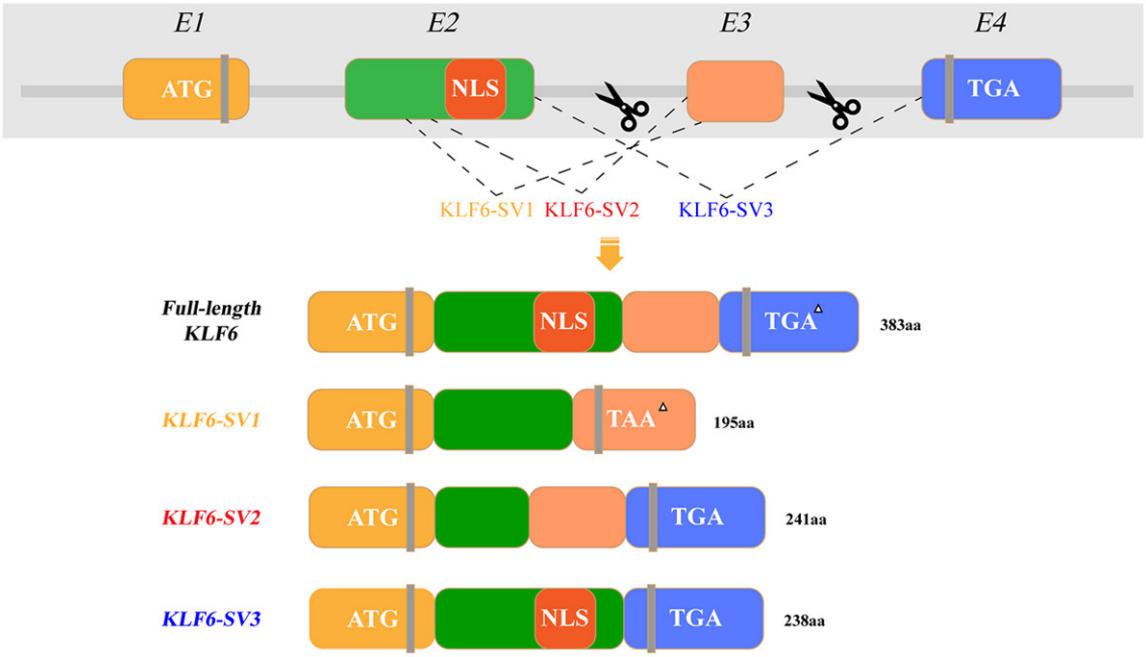

Figure 3. Schematic diagram of the gene structure of KLF6 and its splicing variants. E1-E4 indicates exons 1-4. TGA or TAA represents translation stop codons. NLS, Nuclear Localization Signal. The triangle indicates that the Stop codon is in a different box from the KLF6 open reading box.

secret splice sites in exon 2 and producing the carcinogenic splice isomer KLF6-SV1 (**Figure 3**). KLF6-SV1 lacks the carboxyl-terminal DNA-binding domain and the adjacent 5' basic structure [57, 60]. The functional inactivation of the KLF6 gene and KLF6-SV1 overexpression in tumors can undoubtedly contribute to the deregulation of crucial cellular processes such as proliferation, differentiation, adhesion, death, motility, and invasion (**Figure 4**), all of which lead to cancer.

Roles of KLF6-SV1 in NSCLC formation and progression

KLF6-SV1 increases cancer cell proliferation and survival

Under normal physiological conditions, KLF6-SV1 is ubiquitously present in cells and tissues of the human body. KLF6-SV1 expression is significantly upregulated in numerous malignancies under pathological term conditions and is strongly linked to cell proliferation in cancers such as HCC, lung cancer, ovarian cancer, and glioblastoma.

According to a recent study, Ras activation is transduced to splicing factor ASF/SF2 via the PI3K/Akt pathway and upregulated KLF6-SV1 expression in human HCC samples and cell lines. KLF6-SV1 overexpression inhibits the activity of p21, resulting in cell proliferation. When Ras signaling is inactive, ASF/SF2 primarily produces KLF6, resulting in p21-mediated growth inhibition [72]. In SK-MES-1 cells, we found that high expression of KLF6-SV1 significantly promoted Akt phosphorylation. Simultaneously, the PI3K/Akt downstream protein Cyclin D1 levels were significantly increased, promoting cell proliferation. In A549 cells, knocking out KLF6-SV1 decreased p-Akt levels while decreasing Cyclin D1 expression. Furthermore, Bcl-2 expression increased whereas Bax, cleaved Caspase9, and cleaved Caspase3 expression reduced in SK-MES-1 cells. KLF6-SV1 can promote cell survival by changing the Bcl-2/Bax axis and the caspase cascade [65]. According to another study focused on lung adenocarcinoma (LUAD) cell lines, KLF6-SV1 overexpression increased lung cancer cell proliferation by controlling the Bcl-2 apoptotic family (see the next section) [62].

KLF6-SV1 promotes NSCLC cell proliferation by activating the PI3K-Akt signaling pathway. Furthermore, KLF6-SV1 can maintain lung cancer cell viability by altering related apoptotic

Table 1. The functional roles of KLF6 spliced variants in cancer

Isoforms	Tumor types	Key results	References
KLF6-SV1	Prostate cancer	KLF6-SV1 overexpression accelerates human and mouses prostate cancer progression and metastasis.	[57-59]
	Ovarian carcinoma	KLF6-SV1 up-regulation results in increased proliferation, invasion, angiogenesis, and tumorigenicity.	[30, 60, 61]
	Lung cancer	KLF6-SV1 can regulate Bcl-2 family proteins to inhibit apoptosis and promote cell survival. High expression of KLF6-SV1 can significantly promote the invasion and migration of cancer cells. Targeted inhibition of KLF6-SV1 can restore the resistance of NSCLC cells to cisplatin.	[62-66]
	Gastric cancer	KLF6-SV1 overexpression mediates cell proliferation, survival, angiogenesis, motility, and invasion.	[67]
	Breast cancer	KLF6-SV1 drives breast cancer metastasis and is associated with poor survival.	[68]
	Chronic lymphocytic leukemia	Autologous T cells expressing the oncogenic transcription factor KLF6-SV1 prevent apoptosis of chronic lymphocytic leukemia cells.	[69]
	Nasopharyngeal carcinoma (NPC)	KLF6-SV1 leads to a significant decrease in E-cadherin and thus promotes tumor progression and metastasis in young NPC patients.	[70]
	Hepatocellular carcinoma (HCC)	The expression of KLF6-SV1 is up-regulated not only in the carcinogenic Ras/PI3K/Akt-dependent signal pathway but also in the carcinogenic HGF/PI3K/Akt-dependent signal pathway, thereby changing the relative ratio of KLF6 Full to KLF6-SV1, which in turn leads to increased proliferation of HCC cells.	[71, 72]
	Glioblastoma multiforme (GBM)	KLF6 allelic imbalance, decreased KLF6, and increased KLF6-SV1 expression are common findings in primary GBM tumors, and these changes have antagonistic effects on the regulation of cellular proliferation in GBM cell lines. No significant link between increased KLF6-SV1 expression levels and survival could be found in GBM.	[47, 73]
	Pancreatic cancer	KLF6-SV1 overexpression correlates with prognosis and tumor grade in patients with pancreatic cancer.	[74]
KLF6-SV2	Hepatocellular carcinoma	In hepatocellular carcinoma and the HepG2 cell line, high expression levels of the KLF6-SV2 lead to a significant reduction in cell proliferation associated with apoptosis by activating $p21^{CIP/WAF1}$ and the pro-apoptotic Bax gene, as mediated by the p53.	[75-77]
	Colorectal cancer (CRC)	KLF6-SV2 expression is decreased in CRC and indicates that KLF6-SV2 plays a role as a tumor suppressor in CRC by efficiently blocking cell proliferation, arresting the cell cycle, and inducing apoptosis, which may be related to increased expression of p21 and Bax.	[78]
KLF6-SV3	-	Functions are yet to be elucidated.	-

signaling pathways, thereby indirectly stimulating cell growth (**Figure 5**).

KLF6-SV1 is considered a novel antiapoptotic protein in NSCLC

The death receptor (extrinsic) pathway and the mitochondria-mediated (intrinsic) pathway are two primary signaling pathways that regulate cellular apoptosis [89]. The binding of ligands to cell surface receptors, such as tumor necrosis factor-related apoptosis-inducing ligand receptors and fatty acid synthase, initiates the extrinsic pathway of apoptosis (Fas) [90, 91]. Cell injury initiates the intrinsic apoptosis process, characterized by the release of cytochrome c from the mitochondria into the cytoplasm [92]. The Bcl-2 family proteins have important mitochondrial functions and are classified as either pro-apoptotic proteins (Noxa, Bax, and Bak) or anti-apoptotic proteins (Bcl-2, Bcl-xl, and Mcl-1) [93-97].

According to the current study, KLF6-SV1 overexpression regulates Bcl-2 protein family-related proteins, limiting apoptosis and thus providing tumor cells a growth advantage. KLF6-SV1 overexpression can significantly increase Bcl-2 expression while decreasing Noxa expression, inhibiting lung cancer cell apoptosis [62]. KLF6-SV1 is also substantially expressed in chemotherapy-resistant lung cancer cell lines. When KLF6-SV1 is suppressed by small interfering RNA (siRNA), Noxa and the activity of Caspase3 and Caspase8 are expressed is dramatically increased [63]. SiRNA can also inhibit the anti-apoptotic protein Mcl-1, resulting in a considerable activation of the intrinsic apoptotic pathway (**Figure 5**). As a result, we propose that KLF6-SV1 exists in NSCLC as a novel anti-apo-

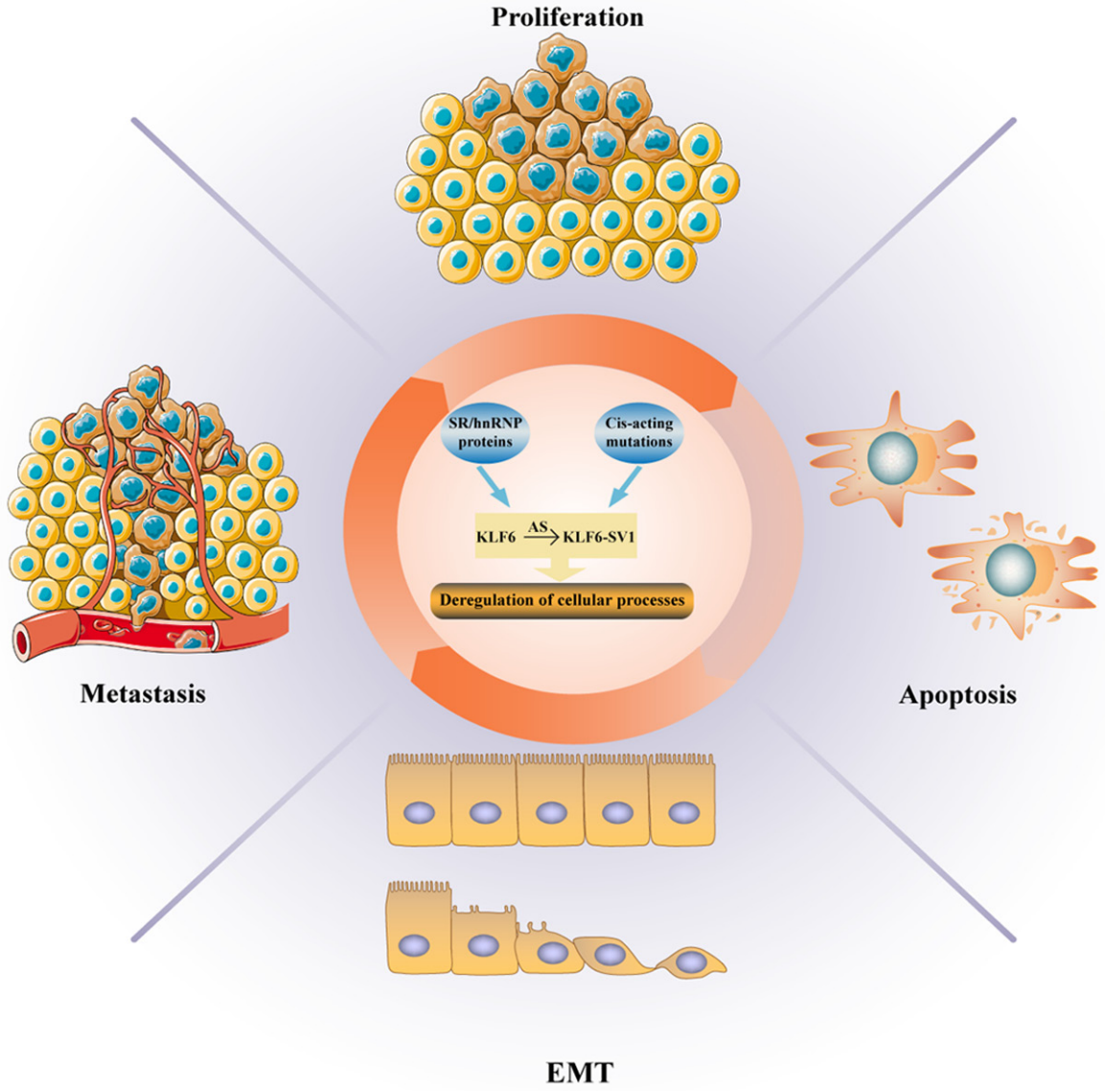

Figure 4. Causes and consequences of splicing pattern alterations. Mutations that alter cis-acting splicing elements can modify messenger RNA (mRNA) quality and protein function. Activating signaling pathways that can affect the activity of splicing regulatory factors or modify the balance between them can also change the proportions of mRNA splicing isoforms. Both can lead to the deregulation of crucial cellular processes such as proliferation, apoptosis, adhesion, motility, and invasion.

ptotic protein that significantly improves LUAD cell survival by inhibiting apoptotic proteins.

Impact of KLF6-SV1 on the epithelial-mesenchymal transition (EMT) and metastasis

The epithelial-mesenchymal transition (EMT) has numerous biological functions in the human body and is frequently observed in multiple tumor types. EMT is considered a key factor in cancer metastasis [98]. By regulating key molecules in linked cell signaling pathways, some splicing factors can regulate the expression of epithelium or mesenchyme during EMT, as well as the incidence and development of malignancies [99].

KLF6-SV1 is significantly associated with EMT markers in estrogen receptor-positive breast cancer by Affymetrix U133A gene chip analysis. Overexpression of KLF6-SV1 results in increased expression of N-cadherin and fibronectin, and decreased expression of E-cadherin, increasing tumor metastatic potential [68]. The impact of KLF6-SV1 on NSCLC cell migration can also be achieved through EMT

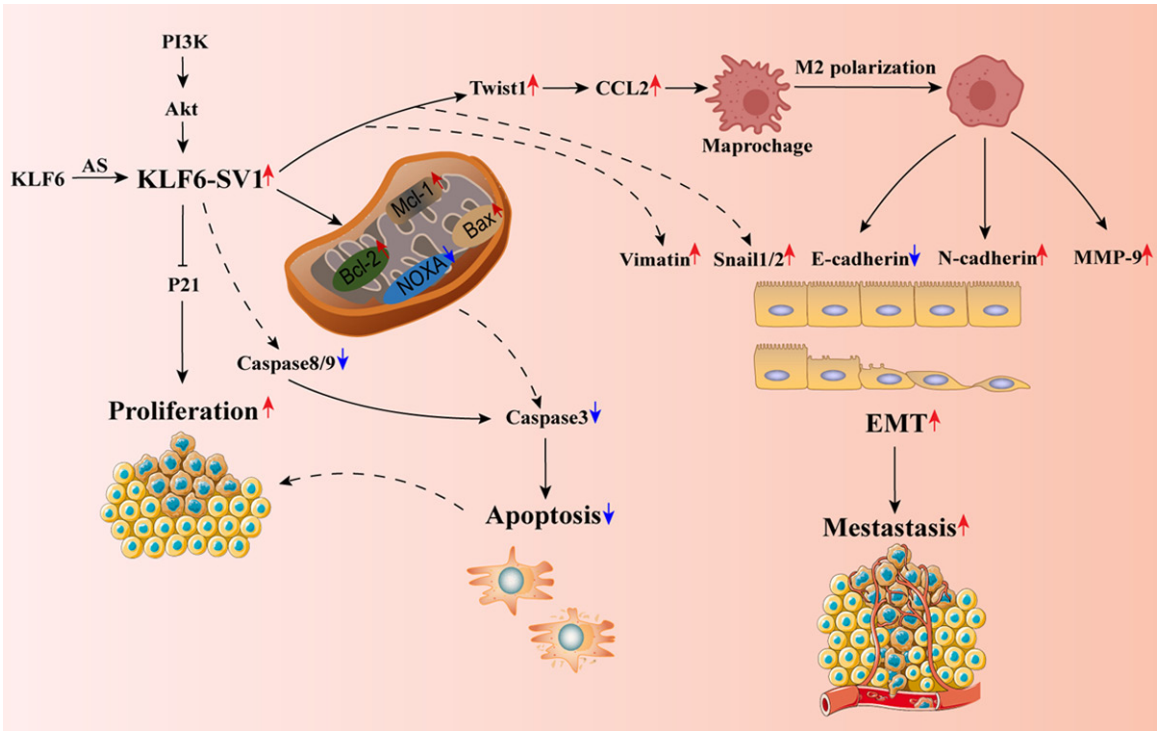

Figure 5. Roles of KLF6-SV1 in NSCLC progression. High expression of KLF6-SV1 promotes cell proliferation via the canonical PI3K/Akt signaling pathway in NSCLC cell lines. KLF6-SV1 can maintain the survival of lung cancer cells by regulating related apoptosis signaling pathways, thereby indirectly promoting cell proliferation. KLF6-SV1 alters the expression levels of EMT-related genes and results in marked cancer cell dissemination.

regulation. KLF6-SV1 can induce macrophage polarization to M2 by increasing the expression of transcription factor TWIST1 and inflammatory chemokine CCL2, promoting lung cancer cell migration [66]. E-cadherin plays a vital role in the formation and growth of cancer as a cell invasion inhibitor, and its absence will result in cellular adhesion failure and tumor metastasis [100, 101]. In KLF6-SV1-upregulated squamous cell cancer cell lines, E-cadherin expression was significantly decreased, whereas N-cadherin, Vimentin, Snail1, and Snail2 expression was significantly increased (**Figure 5**). In contrast, siRNA knockdown of KLF6-SV1 increased E-cadherin expression. This negative correlation indicates that KLF6-SV1 overexpression on E-cadherin may increase the risk of tumor invasion and metastasis *in vivo* and is linked to a poor prognosis in NSCLC patients [65].

KLF6-SV1 is a potential prognostic biomarker in NSCLC patients

Lung cancer is the leading cause of mortality in humans, with NSCLC accounting for over 85% of all cases [102, 103]. Patients with early NSCLC have a 5-year survival rate of more than 70% after surgery. However, the prognosis for patients with advanced NSCLC is only 19% [5, 104]. The prognosis varies greatly even among patients with the same TNM stage. Therefore, the TNM staging system is generally insufficiently predictive [105]. If any biomarkers can be used to forecast the prognosis of NSCLC patients, clinical practice of focused treatment can be better guided, and the goal of improving patient prognosis can be achieved.

KLF6-SV1 is frequently overexpressed in postoperative pathological specimens from patients with primary LUAD. Patients with low KLF6-SV1 expression have a 6.5-year longer median survival than those with high expression, indicating that KLF6-SV1 overexpression is significantly related to postoperative survival in LUAD patients [62]. A multicenter study of patients with node-negative breast cancer shows that higher KLF6-SV1 expression levels are associated with shorter metastasis-free survival [68]. However, researchers do not find a significant association between high KLF6-

SV1 expression and patient prognosis in glioblastoma multiforme (GBM). The main reason may be the generally low survival rate of GBM patients [73]. In an independent cohort study of primary prostate tumors, increased KLF6-SV1 expression is strongly linked to poorer survival. The difference in median survival between high and low KLF6-SV1 expression levels was greater than 4 years [59]. KLF6-SV1 is also found to be substantially elevated in the diseased tissues of 79 patients with lung squamous cell carcinoma and LUAD who underwent complete surgical resection. Our previous studies have linked KLF6-SV1 expression to tumor differentiation, lymph node metastases, TNM stage, and poor prognosis [64]. As a result, KLF6-SV1 has the potential to become a novel NSCLC prognostic biomarker. However, the relevant data presented above are only from a small number of patients. Through multicentred research, we will gather huge volumes of patient data in the future to further confirm our findings.

Potential gene therapy

Over the last few decades, various clinical strategies have been employed to treat NSCLC, including surgery, chemotherapy, radiation, targeted therapy, and immunotherapy [106]. Surgical resection is appropriate for patients with early-stage NSCLC [2, 107]. Chemotherapy primarily centers on antitumor platinum-based medications as a first-line clinical treatment [108]. Despite the extraordinary efficacy of these therapeutic strategies, NSCLC always develops treatment resistance to some degree [109, 110]. Patients with NSCLC now have a poor prognosis. Therefore, a more effective treatment strategy is urgently needed.

SiRNA targeting KLF6-SV1 has been discovered to suppress cell proliferation, invasion, and metastasis in different cancers, including lung cancer [62, 63], glioma [47, 74], prostate cancer [59, 89], and gastric cancer [67]. In LUAD cell lines, siRNA-mediated regulation of KLF6-SV1 expression can effectively cause cancer cell death, which is linked to Noxa overexpression and Bcl-2 inhibition [62]. Moreover, KLF6-SV1 overexpression reduced the apoptosis of cancer cells in patients with NSCLC treated with cisplatin, demonstrating that KLF6-SV1 is linked to cisplatin resistance (**Figure 6**). KLF6-SV1 knockdown using siRNA restores chemosensitivity in drug-resistant NSCLC cells [60, 62]. Similar behavior has been observed in ovarian cancer cell lines. KLF6-SV1 downregulation by siRNA can dramatically decrease ovarian cancer cell migration and proliferation while restoring cisplatin sensitivity in tumor cells [61, 111]. In an *in vivo* model of NSCLC, KLF6-SV1 can inhibit cisplatin-induced changes in apoptotic factors and reverse cisplatin-induced apoptosis [63]. Overexpression of KLF6-SV1, which regulates the apoptotic pathway, could be a new mechanism of cisplatin resistance in NSCLC patients. As a result, treating NSCLC with a combination of siRNA and cisplatin to target KLF6-SV1 can not only reduce chemotherapy resistance and cause chemotherapy-resistant lung cancer cells to die spontaneously (**Figure 6**). The quantity of apoptosis of cancer cells induced by siRNA combined with cisplatin is much higher than any single medication alone, suggesting that siRNA combined with cisplatin could be a new treatment option for chemotherapy-resistant NSCLC.

Problems and prospects

Currently, timely diagnosis and treatment of NSCLC are not satisfactory. More research into the underlying molecular pathways that could improve NSCLC diagnosis and treatment is critical. KLF6-SV1 has previously been demonstrated to be overexpressed in numerous human malignant tumors, and it has a complicated interaction with various malignancies. However, only a few studies with small sample sizes have linked KLF6-SV1 to the occurrence, development, diagnosis, and treatment of NSCLC, and the molecular mechanism of a particular regulation remains unknown. Moreover, aside from the SNP of the KLF6 gene that increases its high expression in cancer, are there other processes or upstream genes that regulate KLF6-SV1 and accelerate the progression of NSCLC? A large sample study in conjunction with multicenter research is still required to better understand how KLF6-SV1 regulates NSCLC.

In both *in vitro* and *in vivo* models of NSCLC, siRNA targeting KLF6-SV1 significantly inhibits tumor cell proliferation and migration [60]. Meanwhile, targeting KLF6-SV1 with siRNA and cisplatin can improve NSCLC cell chemosensi-

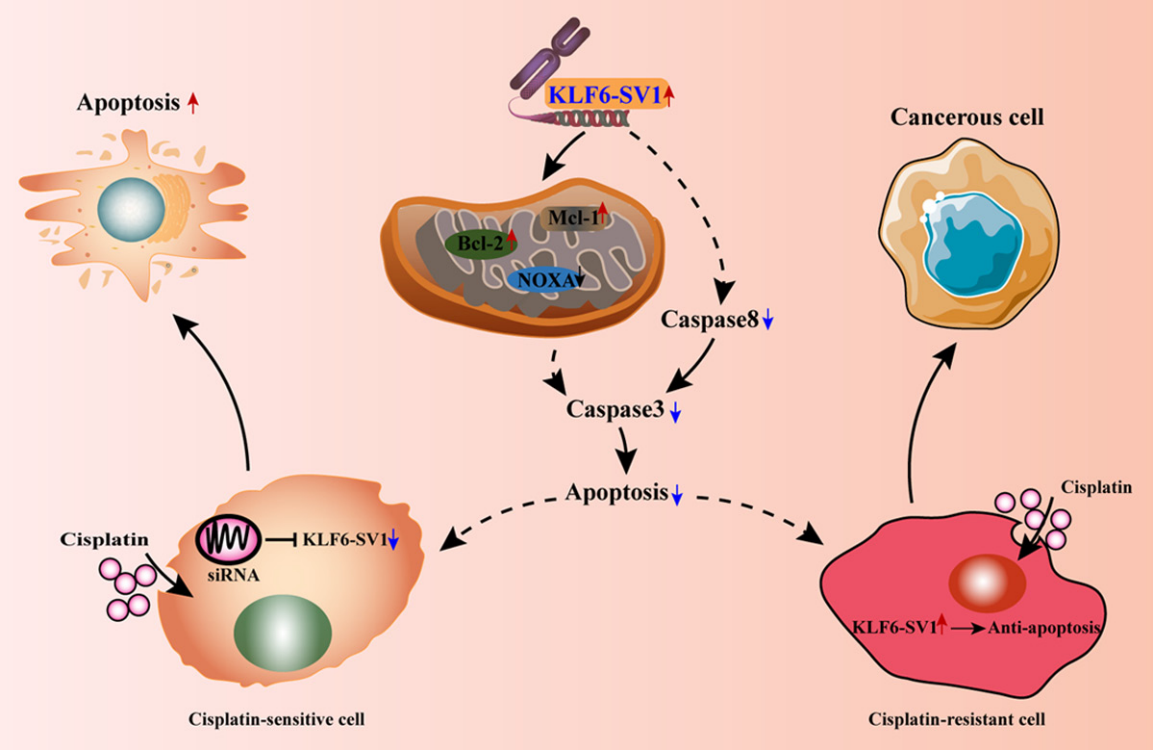

Figure 6. KLF6-SV1-mediated drug-resistance mechanism of NSCLC. Overexpression of KLF6-SV1 abrogates the pro-apoptotic effects of chemotherapy on lung cancer cell lines. Targeted reduction of KLF6-SV1 using siRNA restores chemotherapy sensitivity in resistant lung adenocarcinoma. The combination of siRNA and cisplatin resulted in a significant increase in apoptosis.

tivity, but there are significant challenges in translating these treatment strategies from animal models to human trials [79, 80]. The concept of siRNA therapy has taken many twists and turns since it was first proposed in 1998. In 2001, Elbashir and his colleagues succeeded in suppressing the expression of specific genes for the first time by delivering chemically synthetic siRNA to mammalian cells [112], igniting a research surge. Even though siRNA therapy has long been a source of contentious due to flaws in safety, targeting, efficacy, and transport, recent advances in chemical modification and delivery have resurrected this field as a research hotspot. After decades of research, in 2018, the US Food and Drug Administration (FDA) and the European Commission approved ONPATTRO (patisiran, ALN-TTR02) as the first commercial siRNA treatment for hereditary amyloidogenic transthyretin amyloidosis with polyneuropathy [113, 114]. The FDA recently approved GIVLAARI (givosiran, ALN-AS1) for the treatment of acute hepatic porphyria [115-117]. Fortunately, as the obstacles to the effectiveness of siRNA therapy continue to be overcome, we believe that siRNA therapeutic medicines targeting KLF6-SV1 will quickly enter clinical trials for NSCLC and provide new treatments for patients.

Conclusion

This review briefly described the molecular mechanism by which KLF6-SV1 promotes NSCLC cell proliferation, invasion, metastasis, and anti-apoptosis. It is worth noting that KLF6-SV1 may exist as a novel anti-apoptotic protein in lung cancer cell lines, primarily promoting the malignant development of NSCLC cells by regulating the apoptosis pathway. KLF6-SV1 expression levels in NSCLC patients are strongly associated with tumor differentiation, lymph node metastasis, TNM stage, distant metastasis, and poor prognosis. KLF6-SV1 has the potential to become a new prognostic biomarker in postoperative NSCLC patients. Furthermore, we highlighted the possibility of siRNA-targeted silencing of KLF6-SV1 as a novel strategy for treating chemo-resistant NSCLC patients and its therapeutic potential.

Last but not least, we described some issues in this field and proposed potential solutions.

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Disclosure of conflict of interest

None.

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