Molecules and Cells

Minireview

Decoding SPP1 regulation: Genetic and nongenetic insights into its role in disease progression

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ABSTRACT

Secreted phosphoprotein 1 (SPP1), also known as osteopontin, is a multifunctional glycoprotein that plays a critical role in various physiological processes, including cell adhesion, chemotaxis, immune regulation, and tissue remodeling. Originally identified as a key component of the bone matrix, SPP1 is now recognized for its broad involvement in numerous tissues and significant impact on both normal physiology and disease progression. Dysregulation of SPP1 has been strongly implicated in the pathogenesis and progression of several diseases, including cancer, cardiovascular diseases, autoimmune disorders, and chronic inflammatory conditions. The expression of *SPP1* is tightly regulated by genetic and nongenetic mechanisms. Genetic alterations, such as single-nucleotide polymorphisms, insertions and deletions, and structural variations within the *SPP1* gene, have been associated with increased susceptibility to various diseases, influencing disease severity and outcomes. Additionally, nongenetic regulations, including DNA methylation, histone modifications, and long noncoding RNAs, play crucial roles in modulating *SPP1* expression in response to environmental and cellular signals. This review provides a comprehensive overview of the genetic and nongenetic regulatory mechanisms governing SPP1 and examines their implications in disease pathogenesis. By integrating recent findings, this review highlights the complex interplay between genetic predispositions and nongenetic regulations in determining SPP1 activity and offers new insights into its role as a potential biomarker and therapeutic target. Understanding these regulatory pathways is essential for the development of targeted interventions for diseases in which SPP1 plays a pivotal role.

Keywords: Genetic, Nongenetic, Pathogenesis, Secreted phosphoprotein 1, Therapeutic target

INTRODUCTION

Secreted phosphoprotein 1 (SPP1), also known as osteopontin (OPN), is a multifunctional protein that was first identified as a key component of the bone matrix. OPN is a glycoprotein encoded by *SPP1*, located on chromosome 4q22.1. It is expressed in various tissues, including the bone, kidney, liver, and immune cells, and plays a crucial role in diverse physiological processes (Sodek et al., 2000). SPP1 interacts with multiple cell surface receptors, including integrins and CD44, and mediates a wide range of intracellular signaling pathways that contribute to its role in maintaining tissue homeostasis and responding to physiological stress (Weber et al., 1996).

The importance of SPP1 extends beyond its physiological roles, as its dysregulation has been implicated in a variety of pathological conditions. Elevated SPP1 is commonly observed in chronic inflammatory diseases, cancer, and is thought to contribute to disease progression through its effects on cell proliferation and survival (Lamort et al., 2019; Rittling and Singh, 2015). SPP1's involvement in these diseases is often driven by alterations in gene expression, which can be influenced by both genetic and nongenetic factors. Genetic variants in SPP1, such as single-nucleotide polymorphisms (SNPs), insertions and deletions (INDELs), and structural variations are associated with an increased susceptibility to certain diseases, whereas nongenetic regulations, including DNA methylation, histone modifications, and long noncoding RNAs (lncRNAs), can lead to aberrant *SPP1* expression in response to environmental and cellular signals. Understanding these regulatory mechanisms is critical for elucidating the complex role of SPP1 in disease.

This review provides a comprehensive overview of the genetic and nongenetic mechanisms that regulate SPP1 and their implication in disease pathogenesis and progression. We explore the current understanding of how genetic alterations in

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SPP1 contribute to disease susceptibility and how nongenetic regulations influence its expression in various pathological contexts. By integrating findings from recent studies, this review highlights the genetic and nongenetic factors that modulate SPP1 activity and discusses the potential of targeting these mechanisms for therapeutic interventions in diseases.

Transcriptional Regulation of SPP1 in Physiological and Pathological Contexts

SPP1 is ubiquitously expressed across various tissues and plays a pivotal role in numerous physiological processes, including bone remodeling, immune modulation, angiogenesis, and cell survival. Owing to its involvement in these critical functions, dysregulation of SPP1 is commonly associated with disease progression. The transcriptional regulation of SPP1 is controlled by a complex network of signaling factors, including cytokines, growth factors, environmental cues, and transcription factors (TFs), which converge to modulate its expression (Fig. 1A).

During bone formation, *SPP1* is primarily upregulated as part of the coordinated activity of various extracellular matrix (ECM) proteins, a process driven by the key TF RUNX2 (Komori et al., 1997; Rutkovskiy et al., 2016). RUNX2, a key regulator of osteoblast differentiation and ECM mineralization, binds to the *SPP1* promoter and induces its transcription. In osteosarcoma, RUNX2 overexpression elevates *SPP1* expression, enhancing cell-cell adhesion with pulmonary microvascular endothelial cells and promoting lung metastasis (Villanueva et al., 2019). In addition to RUNX2, HOXB9 has been identified as an upstream regulator of SPP1. The overexpression of HOXB9 reduces cell death and promotes cell proliferation, thereby contributing to the pathogenesis of osteosarcoma (Han et al., 2024). OCT4, a TF known for its role in maintaining pluripotency, regulates *SPP1* expression in gastric cancer and promotes drug resistance and immune evasion by inactivating T cells (Song et al., 2024). In glioblastoma, SPP1 upregulation is associated with the binding of GLI1, which contributes to tumor aggressiveness by promoting sphere formation in glioma cells (Kijewska et al., 2017). In melanoma, NF-κB2 binds to the *SPP1* promoter, leading to enhanced cell proliferation and invasion (Deng et al., 2020). Moreover, MIF-mediated SPP1 upregulation in macrophages plays a crucial role in promoting tumor metastasis and invasion by facilitating macrophage infiltration into the tumor microenvironment in hepatocellular carcinoma (HCC) (Liao et al., 2023).

In summary, transcriptional regulation of SPP1 is orchestrated by a diverse array of TFs. These TFs, including RUNX2, HOXB9, OCT4, GLI1, NF-κB2, and others, collectively influence involvement of SPP1 in various disease processes. Understanding these regulatory networks offers valuable insights into the potential of targeting SPP1 in therapeutic strategies.

Mechanisms of OPN-Mediated Signaling in Pathological Conditions

OPN, a multifunctional protein encoded by *SPP1*, exerts pleiotropic effects through interactions with a variety of receptors, triggering multiple signaling pathways that are pivotal in disease progression (Fig. 1B).

One of the key receptors for OPN is the integrin αvβ3. Upon binding to αvβ3, OPN activates several downstream signaling cascades that promote cell adhesion, proliferation, migration, survival, chemoresistance, and tumorigenesis (Kariya and Kariya, 2022). Notably, OPN-αvβ3 binding triggers the MEKK1-JNK1 and NIK-ERK pathways, leading to the activation of AP-1, which enhances the motility of cancer cells (Kruger et al., 2014). In liver fibrosis, OPN-αvβ3 interaction plays a crucial role in promoting profibrogenic responses in hepatic stellate cells by activating the PI3K-pAkt and NF-κB signaling pathway. This activation sustains collagen-I production, drives hepatic stellate cell activation, and contributes to metabolic reprogramming (Urtasun et al., 2012). Furthermore, this signaling axis facilitates tumor metastasis and immune evasion in HCC (Lu et al., 2020).

In addition to αvβ3, OPN also interacts with the CD44 family of receptors. The binding of OPN to CD44 activates anti-apoptotic signaling pathways and sustains angiogenesis through the PKC-PI3K-Akt signaling axis (Lin and Yang-Yen, 2001; Yan et al., 2023). In esophageal squamous cell carcinoma, the OPN-CD44 interaction with tumor-associated macrophages activates the PI3K-Akt pathway, which promotes inflammation and enhances tumor cell survival (Wang et al., 2024a). In lung cancer, the OPN-CD44 interaction activates the JAK/STAT3 signaling pathway, resulting in the expression of genes associated with epithelial-mesenchymal transition and maintenance of cancer stem cell-like properties (Choi et al., 2017). In colorectal cancer, OPN secreted by tumor-associated cells activates Wnt/β-catenin signaling, inducing CD44v6 expression on cancer stem cells. This upregulation enhances the migratory and metastatic potential, thereby facilitating tumor dissemination and metastases (Todaro et al., 2014).

In summary, OPN interacts with integrin and CD44 to activate signaling pathways involved in various pathological conditions, including immune-related disorders, chronic inflammation, and tumor progression. These interactions highlight the complex role of OPN in disease progression.

Genetic Variants in SPP1 and Their Implications in Disease Susceptibility

Genetic variants, including SNPs, INDELs, and larger structural variations, play a crucial role in modulating gene expression and influencing disease susceptibility. To specifically investigate the genetic variants of SPP1, we focused on small-scale variants such as SNPs and INDELs. These variants provide a direct assessment of functional changes within the gene and offer information from well-established databases. Given our focus on small-scale variants (1-50bp in size), we analyzed the complete set of SPP1 variants using the dbSNP database and categorized them based on their genomic locations (Sherry et al., 2001). A total of 3,829 variants were identified and distributed across the upstream regions, exons, introns, and downstream regions of *SPP1*. These variants, particularly those that alter the reference allele, are linked to disease progression, making them key targets for further investigation (Fig. 2).

Upstream variants, particularly near the *SPP1* promoter, have been shown to influence transcriptional regulation. For

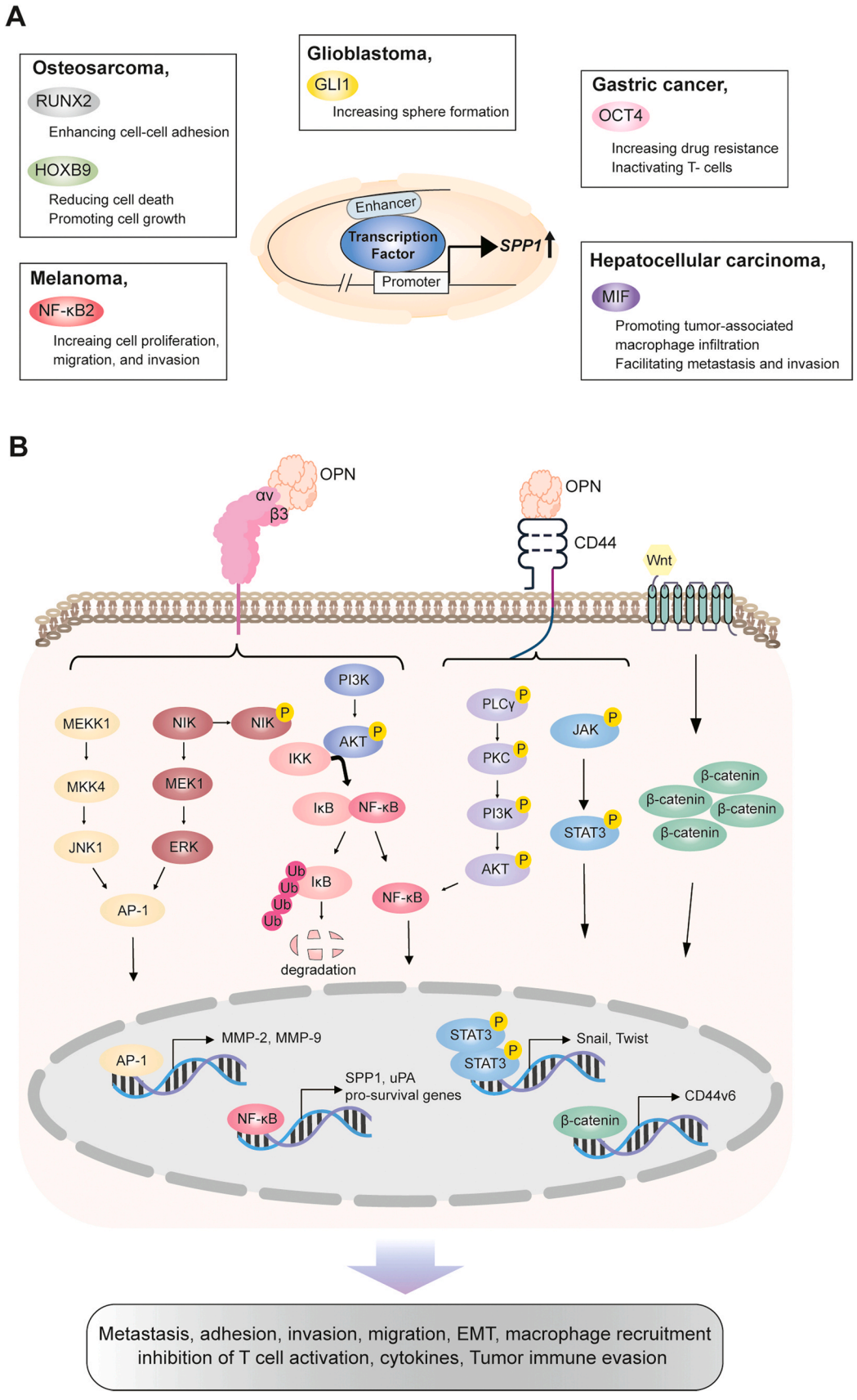

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Fig. 1. Genetic regulation of SPP1 regulated by TFs and the signaling pathway in disease. (A) The expression level of *SPP1* is regulated by various TFs, which are associated with various mechanisms in multiple diseases. (B) Activated OPN binds to αvβ3 integrins and CD44 receptors, activating multiple signaling pathways, such as NIK/MEK/ERK, NFκB signaling, JAK/STAT3, and PI3K/Akt/β-catenin. These cascades regulate the various tumor-promoting genes, like Snail, Twist, MMPs, thereby inducing ECM remodeling, adhesion, invasion, migration, immune evasion, immune suppression, and metastasis.

example, the rs2728127 (A > G) is associated with increased *SPP1* expression and enhanced breast cancer aggressiveness (Ramchandani and Weber, 2013). Additionally, this variant has been linked to abnormal metabolic parameters in cardiovascular disease. In-silico analysis further revealed that rs2728127 can generate binding sites for HSF1, NFκB, and P53 (Perez-Hernandez et al., 2021). Notably, dysregulated HSF1 expression can contribute to cardiac injury, while these factors play key roles in gene regulation processes related to vascular disorders. The T genotype of rs2853744 (G > T) has been linked to a higher risk of HCC in patients with cirrhosis and chronic hepatitis B (Zhang et al., 2016). Similarly, rs11439060 (G > GG) is associated with an elevated risk of cervical cancer, including higher invasion status and tumor differentiation (Xu et al., 2011). This variant is also linked to glioma and oral squamous cell carcinoma, as well as autoimmune conditions, such as rheumatoid arthritis and nephrolithiasis (Chen et al., 2010; Chiu et al., 2010; Xiao et al., 2016). Notably, the G insertion in rs11439060 enhances SPP1 transcriptional activity by creating binding sites for RUNX2 (Giacopelli et al., 2004). In the rs28357094 (T > G) genetic background, glucocorticoids activate glucocorticoid receptor elements, disrupting normal SP1-mediated activation and leading to the chronic overexpression of SPP1 (Vianello et al., 2017). This variant is associated with

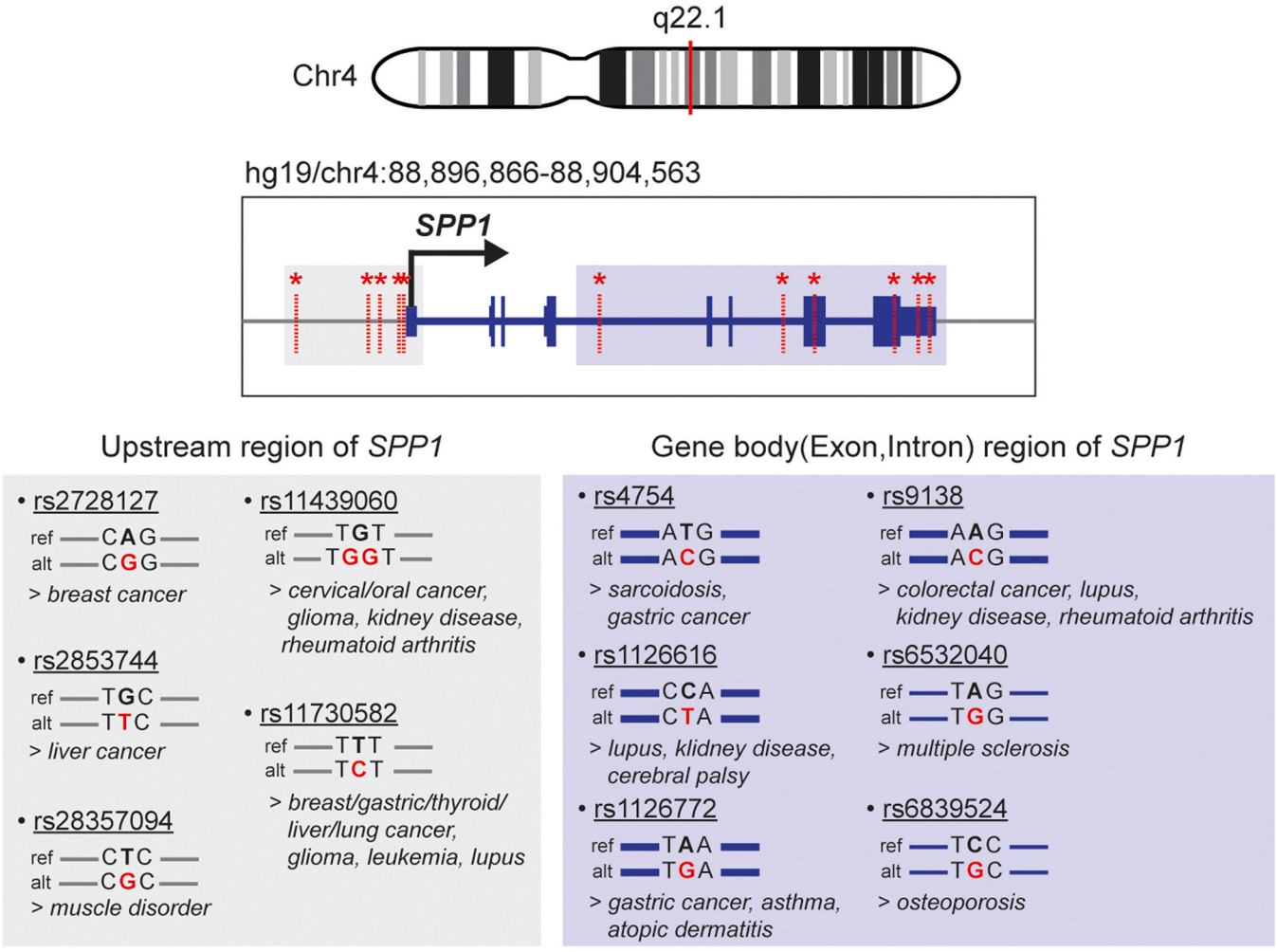

Fig. 2. Genetic variants of SPP1 associated with disease. This schematic diagram illustrates the positions of variants within the genetic region of SPP1. The dashed red line indicates the locations of disease-associated representative variants, as mentioned in the main text. The gene body of *SPP1* is shown in blue, with exons represented as blocks and introns as thin connecting lines. The upstream and downstream regions of *SPP1* are depicted as gray lines. In the lower part of the figure, the DNA sequence changes of representative variants have been summarized by separating the upstream region (gray box) and the gene body region (blue box), and related diseases associated with the presence of these variants are listed.

muscle disorders, including Duchenne muscular dystrophy and juvenile dermatomyositis (Niewold et al., 2010; Pegoraro et al., 2011). The rs11730582 (T > C) is associated with elevated *SPP1* levels and increased cancer risk. The CC genotype correlates with advanced tumor stages in multiple cancers, including breast, gastric, thyroid, gliomas, and acute myeloid leukemia (Chen et al., 2010; Mu et al., 2013; Ramchandani and Weber, 2013; Zhang et al., 2015; Zhao et al., 2012). It is also linked to higher metastasis rates in intrahepatic cholangiocarcinoma and nasopharyngeal carcinoma, as well as systemic lupus erythematosus (SLE) (Trivedi et al., 2011; Wang et al., 2014; Zhao et al., 2014).

Exonic variants in *SPP1* also contribute to disease susceptibility. The rs4754 (T > C) is associated with sarcoidosis and gastric cancer and may influence SPP1 pre-mRNA alternative splicing by altering the binding affinity of exonic splicing enhancers or silencers (Chen et al., 2018; Maver et al., 2009). The rs1126616 (C > T) is significantly associated with SLE, cerebral palsy, and chronic kidney disease (Forton et al., 2002; Kaleta et al., 2019; Shang et al., 2016). It has also been associated with a higher burden of atherosclerosis and an increased risk of cardiovascular events (Cambray et al., 2019). The rs1126772 (A > G) is linked to gastric cancer, and the GG genotype is more common in patients with atopic dermatitis, suggesting an association with inflammatory conditions such as asthma (Kaleta et al., 2021; Qiu et al., 2014). The rs9138 (A > C) is located in the 3′UTR region, a key regulatory site for post-transcriptional gene expression. It has been linked to SPP1 mRNA stability and is associated with an increased risk of colorectal cancer, multiple sclerosis (MS), SLE, rheumatoid arthritis, and chronic kidney disease (Comi et al., 2012; Gazal et al., 2015; Kaleta et al., 2019; Kamal et al., 2017; Trivedi et al., 2011). Intronic variants in *SPP1*, although less studied in terms of direct transcriptional regulation, have been associated with disease severity. The rs6532040 (A > G) influences the severity of MS, highlighting its role in modulating inflammation (Dardiotis et al., 2017). Similarly, the rs6839524 (C > G) has been associated with an increased risk of low bone mineral density in postmenopausal women, which is a key factor in osteoporosis and fractures (Chen et al., 2014).

The precise molecular mechanisms linking SPP1 genetic variants to disease progression remain largely unclear. However, these variants provide insights into potential changes in TF binding sites and mRNA stability. While not all variants directly impact the transcriptional activity, their frequency is strongly associated with disease progression, making them valuable markers of disease susceptibility and prognosis.

Nongenetic Mechanisms Shaping SPP1 in Cancer and Other Diseases

Nongenetic mechanisms encompass epigenetic regulation, including DNA methylation and histone modifications, as well as post-transcriptional regulation, which involves lncRNAs and microRNAs (miRNAs). These mechanisms influence gene expression without altering the DNA sequence, playing a crucial role in disease progression and cellular function (Fig. 3).

DNA methylation is a critical regulator of gene expression that plays a significant role in carcinogenesis. Analysis of the TCGA dataset has revealed that hypermethylation of the *SPP1* promoter is inversely correlated with *SPP1* expression and is associated with more favorable prognoses in adrenocortical carcinoma, gliomas, liver hepatocellular carcinoma, and pancreatic adenocarcinoma (Liu et al., 2022). In contrast, hypomethylation of *SPP1* is linked to its upregulation and poor prognosis in cancers, such as esophageal squamous cell carcinoma, gastrointestinal stromal tumors, thyroid cancer, and lung cancer (Chen et al., 2021; Sang et al., 2020; Tu et al., 2018). In addition to DNA methylation, histone modifications influence gene expression by altering chromatin structure or recruiting histone regulators. In diabetes nephropathy, elevated glucose levels enhance *SPP1* expression, which is strongly associated with an increase in activating histone marks such as H3K4me1, H3K4me3, and H3K9ac, while concurrently decreasing the repressive mark H3K27me3 in the SPP1 promoter region (Cai et al., 2016). In pancreatic carcinoma, increased H3K4me3 deposition at the SPP1 promoter enhances its expression, leading to elevated SPP1 protein levels in both tumor cells and tumor-infiltrating immune cells (Lu et al., 2021).

LncRNAs are critical modulators of nongenetic mechanisms, particularly through post-transcriptional regulation by sponging miRNAs. In particular, lncRNAs that target miRNAs involved in SPP1 regulation play a significant role in various cancers. For instance, in colorectal cancer, lncRNA TP73-AS1 is upregulated and targets miR-539-5p, a negative regulator of *SPP1*. Suppression of miR-539-5p enhances *SPP1* expression, which in turn promotes tumor progression (Ding et al., 2023). Similarly, in pancreatic cancer, lncRNA FOXD1-AS1 acts as a competing endogenous RNA that sequesters miR-570-3p, thereby upregulating *SPP1* and fostering cancer stem cell oncogenesis (Ouyang et al., 2024). In endometrial carcinoma, lncRNA TRPM2-AS1 facilitates tumor progression by acting as a competing endogenous RNA for miR-497-5p, leading to the upregulation of *SPP1*, which enhances angiogenesis and tumor growth (Ma et al., 2024). Additionally, in lung cancer, lncRNA AFAP1-AS1 interacts with miR-3163 to activate the PI3K/Akt/mTOR signaling pathway, driving oncogenic progression (Qiu et al., 2022). In osteoarthritis, lncRNAs, such as MIAT and MALAT1, contribute to *SPP1* upregulation by inhibiting miR-181a-5p and miR-127-5p, respectively, thereby promoting chondrocyte proliferation and apoptosis (Liang et al., 2018; Zeng and Tu, 2022). LINC01133 interacts with Arp3 to stabilize *SPP1* mRNA, preventing its degradation and increasing *SPP1* expression. This elevated *SPP1* contributes to epithelial-mesenchymal transition, particularly in pancreatic ductal adenocarcinoma (Yang et al., 2024).

Given the substantial impact of nongenetic mechanisms on SPP1 regulation, these pathways are potential therapeutic targets. The modulation of DNA methylation, histone modifications, and lncRNAs could offer innovative strategies for mitigating the pathological consequences of SPP1 dysregulation.

Therapeutic Strategies for Targeting SPP1 From Gene Silencing to Protein-Level Inhibition

SPP1 is frequently upregulated in various disease states, particularly cancer and inflammatory conditions, making it a prime

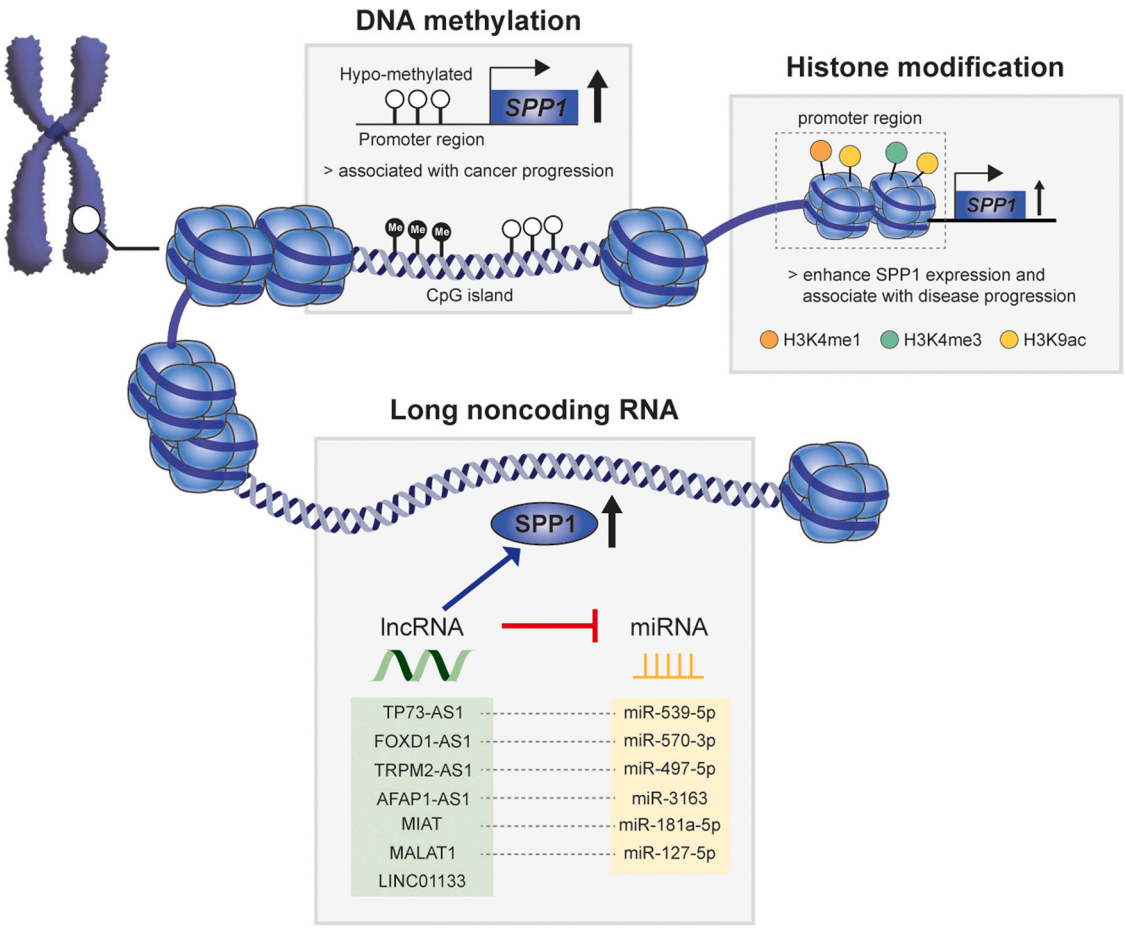

Fig. 3. Schematic representation of nongenetic regulation of SPP1 in disease. This illustration depicts the nongenetic regulation of SPP1, including DNA methylation, histone modifications, and lncRNAs. In DNA methylation, hypomethylation in the promoter region of *SPP1* is associated with disease. Regarding histone modifications, the presence of active histone marks (H3K4me1, H3K4me3, H3K9ac) in the promoter region is associated with elevated SPP1 levels, potentially contributing to disease progression. Additionally, various lncRNAs exacerbate the disease by increasing the expression level of *SPP1* through inhibition of miRNAs (gray dashed lines indicate their association).

therapeutic target. A significant body of research has focused on developing genetically targeted therapies to modulate gene expression. Gene silencing approaches, including small interfering RNA and miRNA technologies, have been employed to inhibit SPP1 at the mRNA level. Specific miRNAs, such as miR-944, miR-181a, miR-181c, miR-127-5p, miR-27a-3p, and miR-433, have been shown to negatively regulate *SPP1* expression in various pathological conditions, thus providing a foundation for therapeutic strategies targeting SPP1 (Bhattacharya et al., 2010; Cheng et al., 2022; Han et al., 2019, 2021; Tu et al., 2016; Zhang et al., 2023). These miRNAs lead to mRNA degradation or translational repression, which in turn could attenuate SPP1-mediated signaling. Although miRNA-based therapies hold promise for the targeted regulation of SPP1, challenges remain with regard to their specificity and stability. To overcome these limitations, more sophisticated approaches such as CRISPR-Cas13-based RNA interference are being explored. CRISPR-Cas13 is a promising technology for targeted RNA degradation that offers high precision and specificity compared with traditional miRNA-based methods (Huang et al., 2022). Recent studies have demonstrated the therapeutic potential of Cas13 in targeting macrophage-derived SPP1 during the inflammatory phase, thereby modulating immune responses and mitigating SPP1-driven pathologies (Wang et al., 2024b). In addition, protein-targeting strategies have also been investigated. Since SPP1 functions through its interactions with various cell surface receptors, inhibiting these interactions at the protein level has emerged as a potential therapeutic strategy. Peptide-based molecules that block SPP1-receptor binding are under development, as these could prevent the activation of downstream signaling pathways involved in cancer cell migration and metastasis (Zhou et al., 2022).

Targeting SPP1 at both the gene and protein levels is a promising therapeutic strategy due to its key roles in immune modulation and ECM remodeling. Advances in gene silencing, RNA-based therapeutics, and protein-targeting methods enable precise control of SPP1 function, potentially improving treatment outcomes across various diseases. Additionally, upstream approaches such as CRISPR-based base editing to correct genetic variants and epigenome editing to modify nongenetic

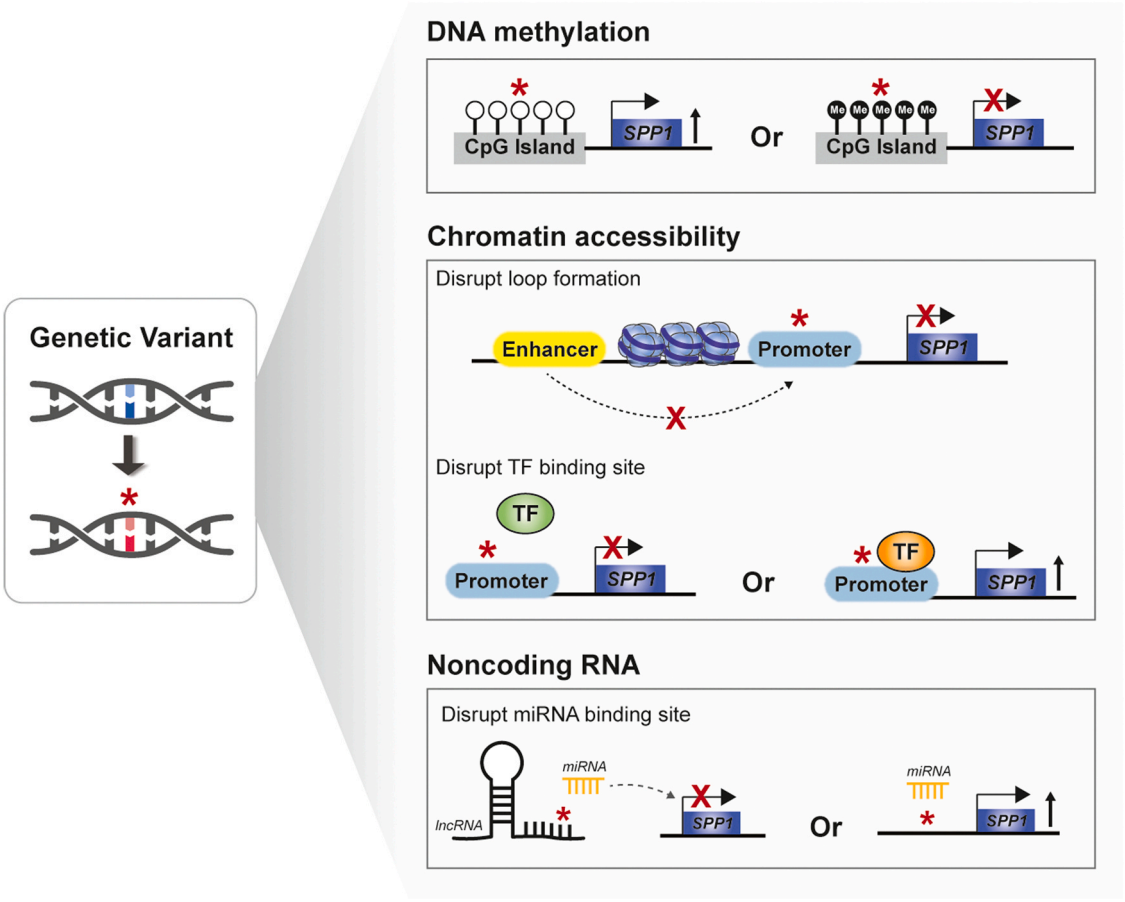

Fig. 4. Schematic representation of the integrated analysis of genetic and nongenetic regulatory mechanisms. This illustration depicts how genetic variants can influence DNA methylation, chromatin accessibility, and noncoding RNA activity. By integrating these regulatory layers, this conceptual framework expands the understanding of how genetic variants impact nongenetic mechanisms in SPP1 and provides insights into potential directions for disease research or therapeutic strategies (red asterisk indicates a genetic variant).

regulatory mechanisms provide more targeted interventions. However, research applying these advanced strategies to SPP1 remains limited, emphasizing the need for further investigation.

CONCLUSIONS

SPP1 is regulated by multiple TFs and plays a pivotal role in normal physiology. However, dysregulation of its genetic control contributes to the disease. Elevated *SPP1* expression is closely associated with disease progression, with SNPs and INDELs in the *SPP1* locus further influencing pathology. Furthermore, nongenetic factors such as DNA methylation, histone modifications, and lncRNAs also regulate SPP1 and correlate with disease outcomes. The complex interplay of these genetic and nongenetic mechanisms underscores the potential regulatory mechanisms as both a biomarker and a therapeutic target in various diseases. In the case of SPP1, this genetic and nongenetic interplay remains unexplored. Variants in CpG-rich regions can influence DNA methylation by introducing or disrupting CpG sites, thereby altering transcriptional activity. Similarly, variants in enhancer or promoter regions can disrupt histone modifications and chromatin accessibility. Moreover, lncRNA-associated variants can impact RNA stability, structure, or miRNA interactions, leading to post-transcriptional regulation changes (Fig. 4). Further research should focus on these genetic and nongenetic interactions to better understand SPP1's regulatory mechanisms in disease pathology.

Future therapeutic strategies should shift from targeting SPP1 directly to focusing on upstream mechanisms, including genetic and nongenetic modifications. By considering their integrated interactions, such strategies offer a more precise and sustainable approach to regulating the fundamental process governing SPP1. When genetic variants disrupt normal gene function, CRISPR-based base or prime editing can restore the original DNA sequence and its function. However, if a variant affects disease through nongenetic mechanisms, such as epigenetic modifications or post-transcriptional regulation, therapeutic strategies should be adjusted accordingly. CRISPR/dCas9-based epigenome editing (eg, dCas9-TET1, dCas9-p300) can modulate DNA methylation or histone modifications to correct variant-induced epigenetic dysregulation. Additionally, genetic variants affecting lncRNAs or regulatory elements, beyond correcting the variant itself, approaches like antisense oligonucleotides to suppress mutant lncRNAs or miRNA mimics/inhibitors to restore disrupted miRNA interactions can enhance efficacy. This dual-targeting approach, addressing

both genetic and nongenetic mechanisms, underscores the need for integrative therapies and the potential of precision medicine informed by multiomics insights.

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DECLARATION OF COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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