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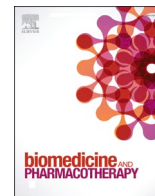
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## Review

# SPARC in hematologic malignancies and novel technique for hematological disease with its abnormal expression

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## ABSTRACT

Secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin or *BM-40*, is a matricellular protein involved in several biological processes including cell adhesion, growth factor availability, extracellular matrix remodeling and immune-regulation. SPARC has also been associated with a variety of diseases including diabetes, colon cancer, and leukemia. The expression of SPARC in different diseases exhibits some degree of ambiguity, especially in hemopathies. Herein, we review the current expression and effects of SPARC in various hematologic disorders with respect to nanoparticle albumin bound innovative therapies and related diagnostic research, providing a clinical perspective on the use of NAB technology in the frontier treatment of hematologic diseases.

## 1. Introduction

Osteonectin or basement-membrane protein 40 (*BM-40*) is a human protein encoded by the secreted protein acidic and rich in cysteine (SPARC) gene, present on chromosome 5q31-q33 [1,2]. It has not only been identified in the adrenal, appendix, bone marrow, gall bladder, placenta, and even the fat and salivary gland, but also in the gut epithelium, liver fibrotic tissues and several tumor cells [3–7].

The human SPARC is a 303 amino acid protein with a molecular weight of 32kD. A 17 amino acids signal peptide is removed during processing of the protein, leaving the mature SPARC protein composed of 3 distinct structural domains. As observed in its structure (PDB code

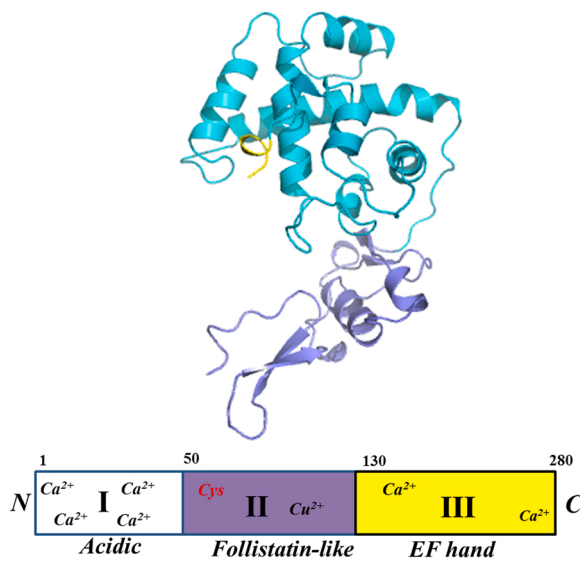
2V53), SPARC is constituted of an N-terminal domain made of 52 amino acids where calcium ions bind, the other domain is follistatin-like located between the N-terminus and the extracellular calcium (EC) binding domain with 10 cysteine and two copper binding sites. The last domain is an EC-binding domain containing a canonical pair of EF-hands that bind to calcium with high affinity [8–10] (Fig. 1).

Normally, SPARC gene appears to regulate cell growth through interaction with the extracellular matrix and cytokines. It positively regulates stabilin-1 through the extracellular epidermal growth factor (EGF). Knockdown of stabilin-1 decreases SPARC expression, while elevated SPARC levels have been linked with stabilin-1 overexpression. It also regulates integrin reaction associated with the extracellular

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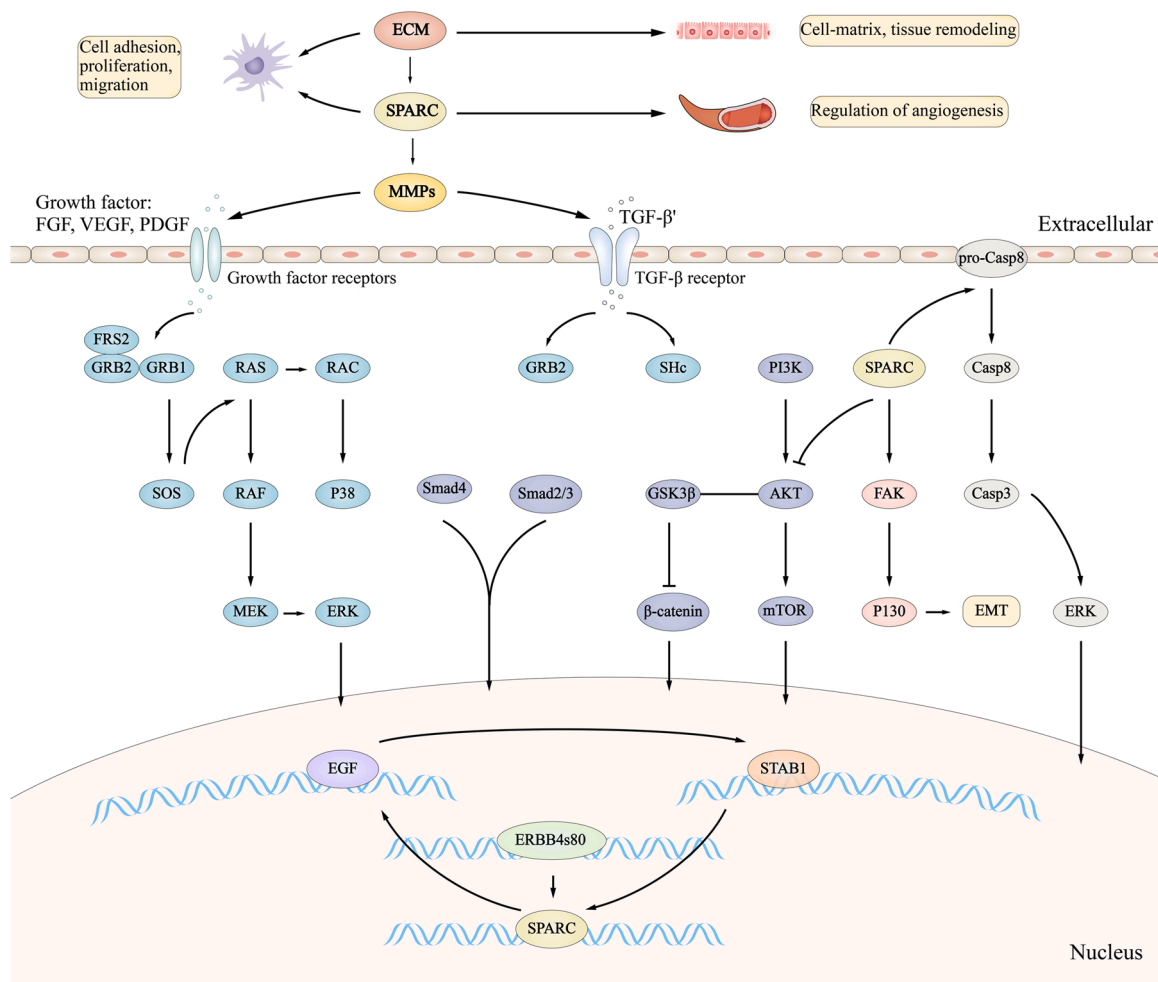


**Fig. 1. : Protein structure of human SPARC.** Three domains are show in box. The yellow in the structure represents EF hand domain with  $Ca^{2+}$  binding; purple is Follistatin-like domain, Cysteine is located at this site; blue is acidic domain with  $Ca^{2+}$  and PDGF binding.

matrix (ECM) and influences integrin linked kinase ( ILK ) which is a downstream element of integrin signalling [11,12]. Moreover, short-hairpin RNAs targeting SPARC reduces the activity of ILK, focal adhesion kinase [13] and protein kinase B (Akt) leading to decreased cell survival and invasion ability [14]. Cell-matrix interactions and tissue remodeling are regulated by SPARC through binding to collagen and other ECM proteins, and activating matrix metalloproteinases (MMPs) and several growth factors like fibroblast growth factor (FGF), transforming growth factor  $\beta$  (TGF- $\beta$ ), vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) [14–17] (Fig. 2).

Hematological malignancies are malignant neoplasms classified into acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myeloma, and lymphoma. It is worth noting that myelodysplastic syndromes (MDS) represent a distinct spectrum of hematological diseases [18]. However, SPARC has been demonstrated to exert varying effects in different hematologic malignancies (Table 1).

Specific to latest information on novel cancer agents and treatment approaches, albumin as an almighty drug carrier in anti-cancer drug delivery system, and nanoparticles-based delivery system has generated great therapeutic expectation to inhibit activity of tumor cells. These studies have established that nanoparticle albumin-bound (NAB) technology is an important method to treat cancer patient. For instance, nanoparticle albumin-bound paclitaxel (nab-paclitaxel) has been used in patients with breast cancer who have failed chemotherapy or are resistant to drugs demonstrated efficacy, even in the non-small-cell lung cancer and pancreatic cancer remain appear favorable efficacy and



**Fig. 2. SPARC associated signaling pathway in this review.** SPARC related pathways are summarized here, mainly related to hematologic diseases.

**Table 1**  
Role of SPARC in hematological malignancies.

Hematological malignancy	Expression	Related therapy	Prognosis	Relevant gene	Reference
DLBCL	Increased SPARC+ SC	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, prednisone	Good	FN1	[24–28]
MM	Increased expression	5-Aza-2-Deoxycytidine, Lenalidomide	Poor	ERK, JNK, p38, NF- $\kappa$ B	[31–34]
5q <sup>-</sup> syndrome	Decreased expression	Lenalidomide	Good	G3BP1, CSNK1A1, VSIG4, PPIC, TPBG	[37–42]
CML	Decreased expression	Imatinib	Good	BCR-ABL, Fyn/ERK	[47–54]
CN-AML	Increased expression	Cytarabine, Daunorubicin	Poor	ILK/AKT/ $\beta$ -catenin, TCF/LEF, SP1/NF- $\kappa$ B, FLT3, DNMTs	[57–63]
ATL	Decreased expression	Bortezomib	Good	VEGF-B, FGF-1	[67,68]
CNSL	Decreased expression	Intrathecal chemotherapy; Intrathecal rituximab	Good	APOD, A2M, APOA1HRG	[72–80]

safety profile [19]. Ovarian cancer patient who received relacorilant plus nab-paclitaxel appear prolong their survival. Nanotechnology has broad implications for coronary artery disease, it may support a safe and effective drug delivery platform for modulating lipid drugs and reducing inflammation and angiogenesis in atherosclerotic plaques and preventing thrombogenesis [20,21].

## 2. The role of SPARC in hematological malignancies

### 2.1. In the diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma is called DLBCL for short, a most common type of non-Hodgkin lymphoma that is derived from abnormal B-cells [22,23]. SPARC is highly expressed in DLBCL evaluated with OncoPrint has confirmed, and the ROC analysis shows SPARC overexpression might be a favorable prognostic biomarker for DLBCL [24]. Similarly, Meyer team found that the tumor microenvironment affects survival in patients with DLBCL. Such patients, no matter the number of SPARC positive cells in the tumor microenvironment had favorable remission rates after rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone therapies in activated B-cell (ABC)-type DLBCL, but not in the germinal center B-cell-type DLBCL [25]. According to clinical data analysis, DLBCL patients have a wide variation in survival index and tumor microenvironment plays a role in determining the survival of DLBCL patients [26].

Recent studies report that the stromal cell (SC) signature could predict the survival of DLBCL patients and the stromal-1 signature reflects a good prognosis, while stromal-2 portends a disadvantageous outcome [27]. Stromal-1 signature included Fibronectin (FN1) and SPARC, high expression FN1 combined with high expression SPARC patients show longer overall survival [28].

As well, the research performed by Meyer's team revealed that DLBCL patients with SPARC<sup>+</sup> SCs had a dramatically longer overall survival compared with patients lacking SPARC expression in SCs (Table 1). Similar to DLBCL patients, ABC-type DLBCL patients with SPARC positivity in the SCs had longer overall survival than SPARC negative ones [25]. Therefore, SPARC expression in SCs in DLBCL is a sensitive indicator to predict the prognosis. This finding suggests that an effective clinical treatment for patients with ABC-type DLBCL lacking SPARC<sup>+</sup> SCs could be a chemotherapeutic vector directly applied to the tumor microenvironment.

### 2.2. In the multiple myeloma

Another manifestation of hematologic malignancy is multiple myeloma (MM). MM is a cancer of the plasma cell, normal plasma cells are derived from white blood cell that helps make up our immune system. Once the immune system is severely attacked, the plasma cells

become cancerous. The malignant plasma cells drive out normal blood cells in the bone marrow, reducing the proliferation of healthy blood cells and producing a monoclonal protein (M protein) or paraproteins [29].

Soluble SPARC can be detected in the plasma of all MM patient and healthy people. The level of SPARC protein expression is significantly higher in serum of MM patient and its methylation will predict poor overall survival in the U266 cells [30], SPARC is associated with migration and invasion of MM cells [31]. In clinical, lenalidomide is a prescription medicine that affects the function of SPARC, use to treat MM patients in combination with dexamethasone [32]. Additionally, 5-Aza-2'-Deoxycytidine and Trichostatin are getting promising result after acting SPARC action [33]. Silencing SPARC expression might be another therapy method to MM patient with SPARC overexpression through decrease phosphorylation of ERK, JNK, p38, NF- $\kappa$ B, and IKK $\beta$  [34].

### 2.3. In the 5q-syndrome

Myelodysplastic syndrome (MDS) with an isolated 5q deletion is named 5q-syndrome [35], laboratory results present normal platelet count, macrocytic anemia or slight thrombocytosis, hypolobated megakaryocytes and less than 5% of blasts in the bone marrow [36]. The 5q-syndrome as a clonal disorder is a somatic hemizygous mutation, G3BP1 and CSNK1A1 were included in deletion of 5q [37]. In humans, SPARC maps to the deleted region in 5q and has been reported to be downregulated in 71% of MDS patients samples [38]. Kerdivel et al. concluded that lenalidomide effectively inhibits the growth of del (5q) erythroid cells without affecting the normal progenitors cells [39].

Lenalidomide treatment of del (5q) cells (500  $\mu$ M) and CD34<sup>+</sup> mononuclear cells from MDS patients increased the expression of SPARC compared with untreated cells. Not only the SPARC gene but also the VSIG4, PPIC and TPBG genes were upregulated by lenalidomide treatment in MDS del(5q) patients (Table 1). More importantly, SPARC expression was only significantly increased in the 5q-syndrome after lenalidomide treatment [40–42].

Pellagatti et al. reported that lenalidomide selectively suppresses the growth of MDS del (5q) progenitors and increases the SPARC expression [40]. Thus, SPARC may be involved in the pathogenesis of the 5q-syndrome, and can also be implemented as a reference target for the efficacy of lenalidomide therapy.

### 2.4. In the chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a chronic malignant hematological disease characterized by an abnormally increased growth of myeloid cells in the bone marrow and accumulation of malignant cells in the blood. The Proliferation of mature granulocytes (neutrophils,

eosinophils and basophils) and their precursors are found in the bone marrow smear in CML [43,44]. The main etiological factor for this disease is a t (9;22) chromosomal translocation involving BCR-ABL, a constitutively active tyrosine kinase (TK) inducing chronic myeloid leukemia [45,46].

Interestingly, SPARC mRNA and protein are downregulated in CML patient cells and treatment of almost 20 patients with IM, which are both tyrosine kinase inhibitors, showed that SPARC mRNA, protein, and serum level was elevated in patients' peripheral blood cells due to monocyte production [47,48]. Besides, SPARC protein levels are decreased in BCR/ABL positive cell lines such as K562, LAMA84 (human chronic myeloid leukemia cell lines), but no difference in SPARC expression has been identified in the BCR/ABL negative acute myeloid leukemia cell line HL60. In addition to the results obtained in leukemia cells, a significant increase in the serum level of SPARC was detected after 18 months of IM treatment. Although, SPARC expression was also reduced in lymphocytes, monocytes, and granulocytes in patients with chronic myelogenous leukemia, but it still increased after IM therapy. Summary of above research illustration, low SPARC express stably in BCR/ABL positive cells and IM treatment induces SPARC overproduction against CML cell proliferation, meanwhile, SPARC expression upregulating may enhance the sensitivity of tumor cells to TKI therapy [49,50]. The exogenous SPARC intraperitoneal or subcutaneous injections into xenograft tumor models, like colon or hepatocellular carcinoma model, were shown to significantly suppress tumor growth [51,52]. Consequently, effective utilization of recombinant SPARC or its derivative peptides may exploit a new approach for the treatment of leukemia. More significantly, SPARC mRNA overexpression was resistant to the BCR-ABL inhibitor imatinib (IM-R cells) [53], research from Fenouille et al. found that SPARC accumulation in cells stimulated Fyn/ERK kinase signaling leading to imatinib resistance in CML (Fig. 2)

[54]. Hence, excessive SPARC accumulation combined with imatinib is counterproductive in treating leukemia. That is why an alternative approach regarding SPARC in imatinib-resistant leukemia therapy is needed (Table 2).

### 2.5. In the acute myeloid leukemia

Acute myeloid leukemia (AML) is a disorder of myeloid cells inducing an abnormally rapid growth of cells in the bone marrow and blood. Cytogenetically normal acute myeloid leukemia (CN-AML) is a type of AML in which patients have a shortage of WBCs, RBCs and granulocytes leading to infection and anemia [55,56].

Analysis of SPARC expression in primary CN-AML patients treated with cytarabine and daunorubicin showed that SPARC overexpression is associated with adverse clinical outcomes in 153 younger CN-AML patients treated with cytarabine daunorubicin-based regimens and increase the proliferation of leukemia cells in AML murine model. In particular, low SPARC expression THP-1 cells, a human monocytic cell line derived from an acute monocytic leukemia patient, which was regulated to overexpression SPARC, after research analysis an increasing THP-1 cell colony forming after SPARC upregulation, all delineated that SPARC promotes the survival and proliferation of leukemia cells, and experiments performed on NOD/SCID/gamma (NGS) mice injected with THP-1/SPARC cells into the tail vein (To upregulate the expression of SPARC) showed hepatosplenomegaly, while the low expression mice model had smaller spleens than control mice. In other words, SPARC overexpression activates leukemia growth and led to more aggressive organic resin [57,58].

To further study the mechanism through SPARC contributes to leukemia cell growth, ILK/AKT/ $\beta$ -catenin signaling pathways were activated. Due to the fact that the secreted SPARC protein has been reported

**Table 2**  
**NAB drugs in Clinical trials.**

Drug	Sponsor	Disease	Phase	Identifier
Nanoparticle albumin-bound paclitaxel	Zhejiang University	Non-small cell lung cancer	Phase 2	NCT02016209
Nanoparticle albumin-bound paclitaxel and carboplatin	The First Affiliated Hospital of Guangzhou Medical University	Non-small Cell lung Cancer	Phase 2	NCT01872403
Nanoparticle albumin-bound Rapamycin	Mayo Clinic	Malignant Neoplasm Endometrial Carcinoma Bladder Carcinoma Breast Carcinoma Cervical Carcinoma Malignant Neoplasm Ovarian Carcinoma Prostate Carcinoma Renal Cell Carcinoma	Early Phase 1	NCT02646319
Nanoparticle albumin-bound rapamycin and pazopanib hydrochloride	University of Washington	Advanced Soft Tissue Sarcoma Locally Advanced Soft Tissue Sarcoma Metastatic Soft Tissue Sarcoma	Phase 1 Phase 2	NCT03660930
Nanoparticle albumin-bound Rapamycin, Temozolomide, and Irinotecan Hydrochloride	Children's Oncology Group	Childhood Solid Neoplasm Recurrent Malignant Solid Neoplasm Recurrent Primary Central Nervous System Neoplasm Refractory Malignant Solid Neoplasm Refractory Primary Central Nervous System Neoplasm	Phase 1	NCT02975882
Nanoparticle albumin-bound paclitaxel plus S-1	Chinese PLA General Hospital	Advanced Pancreatic Cancer	Phase 2	NCT02124317
Gemcitabine+/- Nab-paclitaxel	OncoSil Medical Limited	Unresectable Locally Advanced Pancreatic Carcinoma	Completed	NCT03076216
CORT125134 with nab-paclitaxel	Corcept Therapeutics	Solid Tumors	Completed	NCT02762981
Raltitrexed for injection nab-paclitaxel	Fudan University	Pancreatic Cancer Chemotherapy Effect	Phase 2	NCT04581876
Nab-paclitaxel With Gemcitabine	Emory University	Cancer	Phase 1	NCT03507491
Tilelizumab With Nab-Paclitaxel	Tianjin Medical University Second Hospital	High-Risk Non-Muscle Invasive Bladder Urothelial Carcinoma	Phase 2	NCT04730232
Canakinumab injection; spartalizumab, nab-paclitaxel, gemcitabine	Pancreatic Cancer Action Network	Metastatic pancreatic Ductal adenocarcinoma	Phase 1	NCT03652428
Nab-paclitaxel + Carboplatin/ Nab-paclitaxel + Capecitabine	Hebei Medical University Fourth Hospital	Triple Negative Breast Cancer	Phase 2	NCT04138719
L-glutamine With Gemcitabine and Nab-paclitaxel	Cedars-Sinai Medical Center	Advanced Pancreatic Adenocarcinoma Pancreatic Cancer Pancreatic Ductal Adenocarcinoma	Phase 1	NCT04634539
Gemcitabine + Oxaliplatin + Nab-paclitaxel	Istituto Clinico Humanitas	Cholangiocarcinoma	Phase 1 Phase 2	NCT03943043
CPI-613 With Gemcitabine and Nab-paclitaxel	Atlantic Health System	Pancreatic Cancer Metastatic Pancreatic Cancer	Phase 1	NCT03435289

to interact with diverse cell surface receptors, some membrane integrins are involved. A multifunctional cytoplasmic serine/threonine kinase (ILK) was found to be activated by this interaction, and AKT was found phosphorylated and activated through ILK, but GSK3 $\beta$  (glycogen synthase kinase 3 $\beta$ ) which induced  $\beta$ -catenin degradation and translocation into the nucleus was phosphorylated and inactivates. Indeed, up-regulation of the *TCF/LEF* target gene *MYC* supports *SPARC*-induced  $\beta$ -catenin-*TCF/LEF* activity in AML cells [57,59–61].

The mechanism of *SPARC* overexpression in AML blasts is associated with network *SP1/NF- $\kappa$ B* and miR-29b modulation. Thus, activation of *SP1/NF- $\kappa$ B* and inhibition of miR-29b are responsible for *SPARC* impairment. Similar mechanisms have been identified in oncogenes involved in AML such as *KIT*, *FLT3* and *DNMT3* (Fig. 2). On the other hand, *SPARC* was low or absent in AML with *MLL* rearrangements. JF Dimartino's group evaluated the *SPARC* function in AML patients and cell lines with *MLL* rearrangements by microarray analysis and discovered that *SPARC* was downregulated in AML cells with *MLL* gene rearrangement. Further studies showed that *SPARC* induces the apoptosis of AML cell lines with *MLL* gene rearrangement and inhibits progression from G1 to the S phase in *SPARC* sensitive ML2 cells (AML cell line). *SPARC* downregulation is associated with increased dense promoter methylation in ML2 and THP-1 cells (a human monocytic cell line). Thus, observation of *SPARC* expression could facilitate the prediction of AML outcomes, suggesting that *SPARC* is a potential therapeutic target for AML [62,63].

## 2.6. In the adult T-cell leukemia

Adult T-cell leukemia is rare cancer and a type of non-Hodgkin lymphoma, which is usually associated with human T-cell lymphotropic virus type 1 (HTLV-1) infection. Bortezomib is a proteasome inhibitor used to treat mantle cell lymphoma and ATL [64–66].

Ohyashiki group reported that the mechanism of action through which bortezomib induces ATL cell apoptosis is associated with siRNA mediated *SPARC* inhibition. During their study, *SPARC* expression was decreased in ATL cell and TaY cells after transfected *SPARC* enhance the apoptotic effect of bortezomib on malignant cells, confirming that downregulation of *SPARC* promotes the effect of bortezomib in ATL cell death. Even if this study is partially perfect, the results still provide reference for *SPARC* related ATL. Additionally, *SPARC* is overexpressed obtained from HTLV-1 asymptomatic carriers ATLL patients [67]. Previous studies have illustrated that *SPARC* is positively correlated with *VEGF-B* (Vascular endothelial growth factor B) and *FGF-1* (Fibroblast Growth Factor 1) ( Table 1 ), *SPARC* iRNA induced caspase3 promotes the apoptotic effect of bortezomib with concurrent derived *VEGF-B* and *FGF-1* inhibition [68].

Drawing a conclusion from the above performance results, bortezomib suppresses the proliferation of ATL cells via *SPARC* downregulation, indicating that *SPARC* targeted therapy is effective in the treatment of ATL patients, but also various types of cancer responsive to bortezomib.

## 2.7. In the central nervous system leukemia

Acute lymphocytic leukemia is more prevalent in children and affects white blood cells. It progresses aggressively and quickly, with central nervous system (CNS) relapse being a major cause of death [69]. At present, intrathecal chemotherapy or intrathecal rituximab is commonly used in clinical treatment, its curative effect and prognosis are not satisfactory [70,71].

Mo et al. found that *SPARC* expression was significantly downregulated in the cerebrospinal fluid (CSF) of pediatric patients diagnosed with ALL and CNS involvement [72,73]. *SPARC* downregulation correlates with higher complete remission (CR) rates during CNSL treatment. Furthermore, the heatmap and string analysis displayed downregulation of *SPARC* stimulates a decrease in apolipoprotein D (*APOD*), alpha-2-macroglobulin (*A2M*), apolipoprotein A1 (*APOA1*) and an

increase in histidine rich glycoprotein [74]. These five genes interact to form different pathways and function, the repair and development of the nervous system depend on *APOD* in glial cells to regulate lipid migration and avoid cellular oxidative stress [75], *A2M* normally product by hepatic Kupffer cells, it enables suppress tumor cell migration, proliferation, and invasion in astrocytoma malignancy when *A2M* interact with lipoprotein receptor related protein-1 (LRP1) [76,77]. In addition, *HRG* keeps high levels in plasma and acts as an acute phase reactant, it suppresses tumor probably by inducing cell apoptosis and enhancing chemotherapy by promoting vessel normalization and antitumor immune responses [78,79]. All in all, *SPARC* downregulation may be associated with a favorable prognosis of CNSL and *SPARC* represents a promising prognostic biomarker of CNS-involved ALL [72,80] ( Table 1 ).

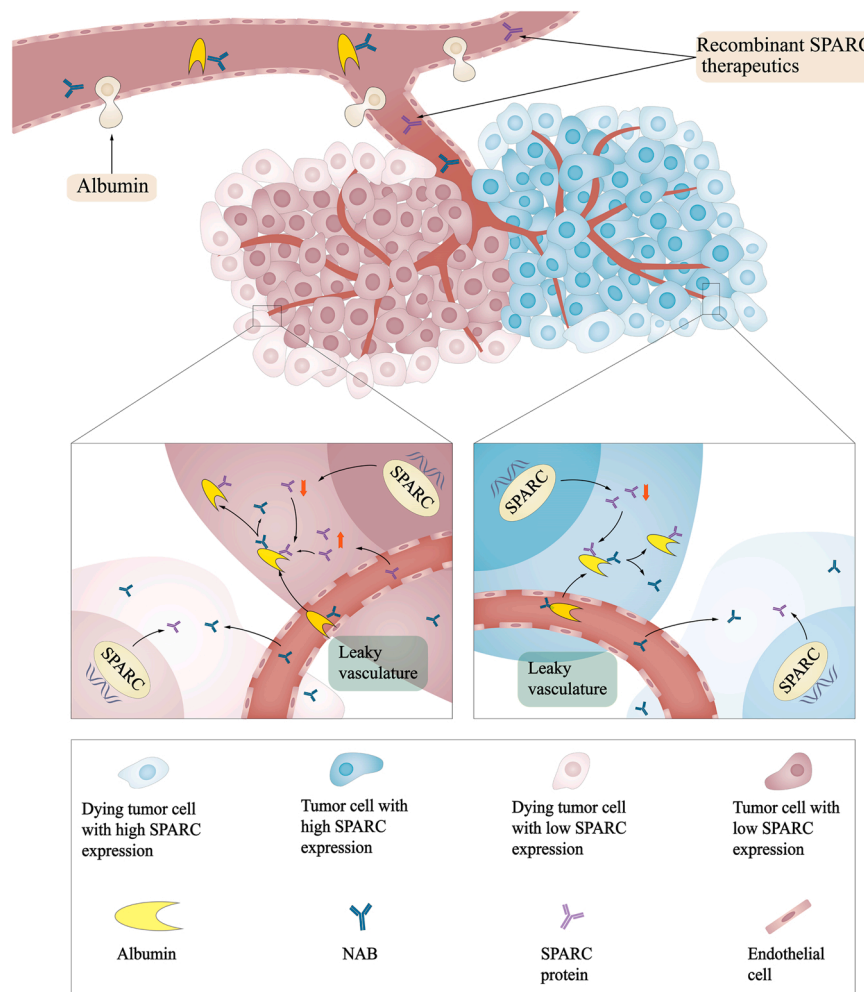
## 2.8. New front therapies targeting SPARC

Given the different expressions of *SPARC* in various diseases, the selection of drugs and therapeutic schemes is not targeted and traditional therapy is limited. Therefore, it is necessary to develop new therapeutic methods to effectively cure *SPARC* relevant diseases.

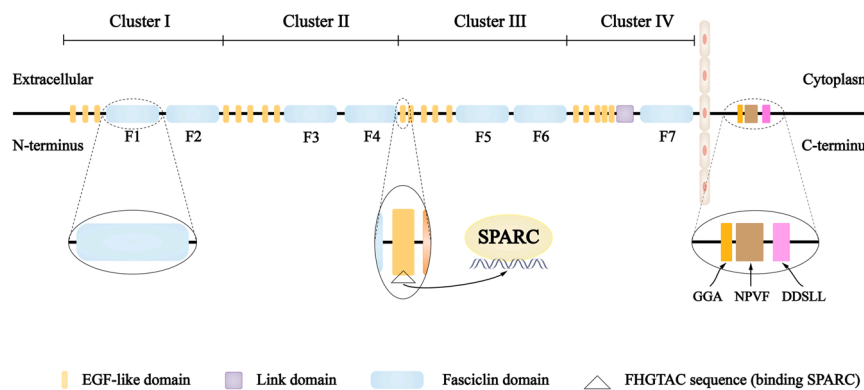
Nanoparticles are one hundred to ten thousand times smaller than human cells, because of it similar in size to enzymes and receptors, nanomaterial can easily penetrate most cells and rapidly interact with large biomolecules on both the surface and inside cells. By gaining access to various areas of the body, nanotechnology approaches are employed to deliver therapeutic agents to treat malignant tumor [81, 82].

Recent thousands of nanoparticle albumin bound (NAB) advances in the research on clinical trials have created. Here, we only present fewer trials in Table 2 as an example. NAB paclitaxel has entered clinical trials for patients with advanced non-small cell lung cancer, and achieved a longer overall survival compare with traditional chemotherapy [83,84], and NAB-paclitaxel plus gemcitabine phase II clinical trials are currently ongoing for *SPARC* overexpress patients with pancreatic cancer, higher response rate and longer progression free survival were illustrated in this stage [85,86]. The technical principle behind NAB drugs relies on the ability of albumin to cross tumor blood vessels and link anti-cancer drugs to albumin promote their tumoricidal activity [87,88]. Most importantly, the affinity of albumin to *SPARC* in *SPARC* overexpressing cancers would permit NAB paclitaxel to target non-small cell lung cancer, pancreatic cancer and head and neck neoplasm, which may lead to better efficacy and improve survival rate [89,90]. Furthermore, NAB drugs can also be used in cancer patients with low *SPARC* expression, if *SPARC* accumulates in malignant cells after the administration of recombinant *SPARC* therapeutics, NAB drugs could reduce excessive *SPARC* accumulation ( Fig. 3 ). The other newest study is silica-templated eumelanin-silver hybrid nanoparticles (MelaSi-Ag-NPs) [91], with human serum albumin is disclosed as an efficient and practical strategy to improve photostability and to perform *SPARC* mediated internalization in breast cancer cells [92–95]. All the above effect may occur in leukemia patients with *SPARC* abnormal expression. Hence, NAB drugs can assist chemotherapeutic drugs located specifically targeting tumor sites.

On the other side, it has been reported that integrins  $\alpha 5$  and  $\beta$  could mediate the expression of *SPARC* [96,97]. Byzova reported that integrins  $\alpha 5$  and  $\beta$  promote *SPARC*'s regulation of malignant cell migration and that the autocrine loop of *VEGFR-2* is also involved in this process [98]. Using phage display, Kzyshkowska et al. noticed that stabilin-1 mediates *SPARC* expression via EGF-like (the extracellular epidermal growth factor) domains including FHGTAC sequence and that a decrease in stabilin-1 reduces *SPARC* expression [11,99] ( Fig. 4 ). The research carried out on nasopharyngeal carcinoma (*NPC*) cells showed that *SOX-5* shRNA (*SRY-Box Transcription Factor 5*) led to a significant increase in *SPARC*. The ability of *SOX-5* to bind directly to the *SPARC* promoter accounts for it being an important transcription suppressor of



**Fig. 3. Nanoparticle albumin bound (NAB) drugs treat SPARC related disease.** NAB binds to albumin suppress malignant cell proliferation in SPARC overexpress cancer. NAB reduced SPARC expression when recombinant SPARC treat low SPARC expression related cancer. NAB mainly binds albumin cross tumor blood vessels to reduce SPARC expression.



**Fig. 4. Stabilin-1 regulates SPARC expression.** Stabilin-1 as a cellular receptor regulates SPARC, and it interrelates with SPARC through EGF-like domain, FHGTAC sequence is included in this domain.

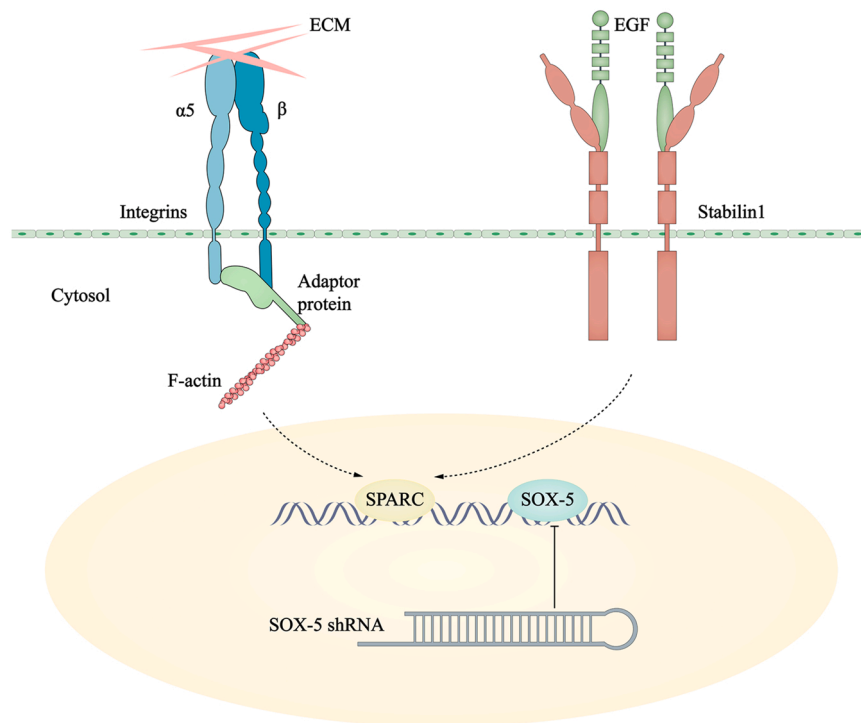
SPARC [100,101]. Based on these facts, SOX5 shRNA could be another creative method to treat leukemia ( Fig. 5 ) .

**3. Conclusion and perspective**

SPARC plays a significant role in different types of cancers and has been shown to have an impact on treatment efficacy and overall

prognosis. Among other functions, SPARC regulates cell-matrix or cell-cell interactions, inhibits cellular growth and migration, which are all properties prompting its evaluation concerning for to the pathogenesis and treatment of various cancers [102,103].

SPARC overexpression has been depicted in gliomas, melanomas, and skin cancer, and has been correlated with adverse outcomes in CN-AML [103,104]. Conversely, SPARC knockdown has been identified to



**Fig. 5. SOX-5 bind to SPARC promoter modify its expression.** Stabilin-1 and integrins  $\alpha 5$  and  $\beta$  mediate effect of SPARC. shRNA of SOX-5 in NPC cell increased SPARC, while SOX-5 bind to the SPARC promoter directly, cause SOX-5 as a significant transcriptional repressor of SPARC.

suppress the proliferation of ovarian and cervical cancerous cells [105, 106], meanwhile low or absent expression is associated with a poor prognosis in colon cancer and some hematological malignancies [73, 107, 108]. In parallel with this, SPARC enable to be as a new potential marker of Myeloid-derived suppressor cells (MDSC) to inhibit MDSC activity to control serious inflammatory state through the regulate of NF- $\kappa$ B signaling pathway [109]. Therefore, previous studies have reported that SPARC is a potentially effective therapeutic target and predictor of the prognosis in leukemia patients. In the Recent studies on NAB drugs, stabilin-1, integrins  $\alpha 5/\beta 3$  and SOX5 shRNA could be referenced for novel therapeutic strategies of leukemia, or nanoparticle chimeric integrin  $\alpha 5/\beta 3$  and SOX5 shRNA designing targeted drugs that inhibit SPARC active sites may also be another effective treatment approach for hematosis with SPARC overexpression. Furthermore, regarding hematopoietic P53 mutations associated with low survival rates in AML and ALL patients, SPARC directly interacts with P53 to mediate cell survival. Studying SPARC and P53 interaction pathways in various types of leukemia may form the foundation for the exploration of new effective therapies, and the synthesis of SPARC/P53 dual target drugs bound to nanoparticle albumin might be a creative treatment for diseases other than leukemia. To investigate another potential treatment, the CRISPR/Cas9 technology can be applied to GM NGS (Genetically modified NOD Prkdc<sup>scid</sup> Il2rg<sup>-/-</sup>) mice as patient derived xenografts (PDX) models of human hematologic malignancies to explore the mechanism of action in SPARC targeted therapy [110].

Considering various studies about SPARC in various malignant diseases, the development of biotherapy and SPARC-targeted drugs will be beneficial for the treatment of relevant diseases. In spite of CRISPR/Cas9 technology only performing on mice models, human trials are a long way off due to unpredictable side effects. Therefore, it opens the possibility of creative therapeutic approaches for enlightening research. The design of targeted drugs for hematologic malignancies is more challenge than that for solid tumor, because SPARC shows great binding affinity to albumin, its binding to albumin caused the enrichment Nab-paclitaxel accumulation in SPARC positive tumors and promotes its anticancer effects, but not in SPARC express negative cancer as we

previously discussed. Obviously, nanoparticle albumin bound (NAB) technology will be applied extensively in the field of hematological malignancy precision therapy in the future in order to require better therapeutic effect and physical safety. Looking forward to study on SPARC has relationship with MDSC, I believe SPARC, as a sensitive indicator to test Myeloid-derived suppressor cells, will be of significant assistance in detecting the prognosis of inflammation.

#### CRediT authorship contribution statement

Wrote or contributed to the writing of the manuscript: QN, QL, ZY-H, CY, JW-L, MY-L. Revised or contributed to revising of the manuscript: F-R-L, JH-Z, CL, JY-S, LY-Z, JT.

#### Conflict of interest statement

This paper has not been published elsewhere in whole or in part. All authors have read and approved the content, and agree to submit it for consideration for publication in your journal. There are no ethical and legal conflicts involved in the article.

#### Data availability

No data was used for the research described in the article.

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