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Review Article

6-O-endosulfatases in tumor metastasis: heparan sulfate proteoglycans modification and potential therapeutic targets

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Abstract: Metastasis is the leading cause of cancer-associated mortality. Although advances in the targeted treatment and immunotherapy have improved the management of some cancers, the prognosis of metastatic cancers remains unsatisfied. Therefore, the specific mechanisms in tumor metastasis need further investigation. 6-O-endosulfatases (SULFs), comprising sulfatase1 (SULF1) and sulfatase 2 (SULF2), play pivotal roles in the post-synthetic modifications of heparan sulfate proteoglycans (HSPGs). Consequently, these extracellular enzymes can regulate a variety of downstream pathways by modulating HSPGs function. During the past decades, researchers have detected the expression of SULF1 and SULF2 in most cancers and revealed their roles in tumor progression and metastasis. Herein we reviewed the metastasis steps which SULFs participated in, elucidated the specific roles and mechanisms of SULFs in metastasis process, and discussed the effects of SULFs in different types of cancers. Moreover, we summarized the role of targeting SULFs in combination therapy to treat metastatic cancers, which provided some novel strategies for cancer therapy.

Keywords: SULF1, SULF2, HSPG, metastasis, therapeutic target

Introduction

Cancer is a serious public health challenge and the second leading cause of global mortality [1]. With earlier diagnosis, advances in local disease management and adjuvant therapies, the overall survival of patients with many solid cancers has increased [2, 3]. However, metastatic diseases are still incurable to a large extent, which are responsible for over 90% of cancer-associated mortality [4-6]. The activation of invasion and metastasis is a crucial hallmark of cancer, but the understanding about specific process and mechanism of metastasis remains limited [7].

Metastasis is a multistep cell-biological process characterized by a series of molecular and phenotypic alterations, facilitating the dissemination and colonization of cancer cells from a primary tumor to distant organ sites [8, 9]. Briefly, tumor metastasis process can be divided into 7 steps: 1) epithelial cells in primary tumors invade locally through surrounding extracellular matrix (ECM) and stromal cell layers, 2) intravasate into the lumina of blood vessels, 3) survive the rigors of transport through the vasculature, 4) arrest at distant organ sites, 5) extravasate into the parenchyma of distant tissues, 6) initially survive in these foreign microenvironments in order to form micro metastases, and 7) reinitiate their proliferative programs at metastatic sites, thereby generating macroscopic, clinically detectable neoplastic growths [6, 9-11]. Each step of the invasion-metastasis is driven by the acquisition of genetic and/or epigenetic alterations within tumor cells and the interaction of nonneoplastic stromal cells. Firstly, mutations of some cancer-associated genes initiate and promote metastasis. Notably, the loss of cancer suppressor p53 or the mutation of proto-oncogene EGFR could allow cancer cells to acquire characteristics that are conducive to metastasis [12, 13].

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Secondly, some signaling pathways that can promote metastasis are activated in the process of late-stage cancer metastasis, such as TGF-β and WNT/β-catenin signals [14, 15]. Thirdly, cancer cells in invasion-metastasis cascade may undergo morphological changes and develop mesenchymal phenotypes [7, 16]. Moreover, the modulating of tumor microenvironment can impact metastasis as well, which is associated with immune cells and stromal cells [17, 18].

In recent years, much attention has been paid to exploring novel molecules which can impact receptor binding and signal transduction. Heparan sulfate proteoglycans (HSPGs) are classical co-receptors for numerous heparan sulfate (HS) binding growth factors and cytokines, thereby influence receptor complex formation and cell signaling [19-21]. The 6-O-endosulfatases (SULFs), including SULF1 and SULF2, are enzymes which selectively remove 6-O-sulfate groups from HS [22]. Consequently, SULFs can modulate structure and function of HS and regulate some critical biological pathways [23, 24]. Dysregulation of SULFs has been reported in numerous cancers, correlating with tumor metastasis [25, 26]. In this review, our primary focus is the comprehensive analysis of SULFs' functions in the process of tumor metastasis, aiming to offer potential therapeutic strategies for metastatic cancer.

The structure and function of HSPGs and SULFs

HSPGs are evolutionarily ancient subclass of proteoglycans which are composed of core protein and covalently attached HS glycosaminoglycan chains [27-29]. Based on their subcellular location, HSPGs are divided into three categories: extracellular HSPGs, exemplified by perlecan and type XVIII collagen; membranal HSPGs, represented by syndecans and glypicans; and the sole intracellular HSPG, serglycin [28, 30, 31]. HSPGs can bind to numerous bioactive molecular ligands, act as scaffolds for protein connections, and regulate receptor complexes formation by their HS chains [32, 33]. Therefore, the structure and modification of HS chains become key points of HSPGs biological functions [33, 34]. Following their biogenesis in endoplasmic reticulum and Golgi apparatus, HS chains experience various of modifications including N-deacetylation and N-sulfation, epimerization and O-sulfation. Subsequent post-synthetic modifications are catalyzed by heparinase and SULFs. Among them, heparinase cleave HS chains at the level of glucuronic acid residues, while SULFs catalyze the hydrolysis of 6-O sulfates [35]. These processes influence the interaction of HS chains and their ligands, thereby modulating a series of biological behaviors including cell growth and adhesion, as well as tumor progression and metastasis [36] (**Figure 1A**).

SULFs attracted researchers' attention in 2001 when Dhoot G.K. et al. identified SULF1 and discovered that SULF1 could regulate HSPG-dependent WNT and FGF signaling by releasing them from HSPGs [37, 38]. Subsequently, a closely related protein which shared similar structural domain with SULF1 was identified as SULF2. Both SULF1 and SULF2 are heterodimers linked by disulfide bond, and studies have revealed that SULFs are initially synthesized as preproproteins, then cleaved into N-terminal 75-kDa subunits and C-terminal 50-kDa subunits by furin-type proteinase [39, 40]. SULFs are composed of three functional regions: the N-terminal sulfatase catalytic regions, the hydrophilic domain (HD) which bind to HS chains, and the end of C-terminal subunits which have significant homology to glucosamine-6-sulfatase and play roles of specific recognition regions [35, 41, 42] (**Figure 1B**). After secreted into extracellular matrix (ECM), SULFs participate in modifications of HS chains and regulate the HS-dependent cell signaling. SULFs can modulate not only FGF and WNT signaling, but also the HS-binding growth factors family like hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), Transforming growth factor-β (TGF-β), and some downstream pathways such as AKT, MAPK, NF-kB, etc. Numerous previous studies have verified the significant roles of SULFs in tumor initiation and progression [25, 43-45].

Despite similar structure and substrate specificity of SULF1 and SULF2, the pathological function of these two enzymes in cancer is distinct [46, 47]. Previous studies have revealed the oncogenic roles of SULF2 across various cancer types [40, 41]. However, the role of

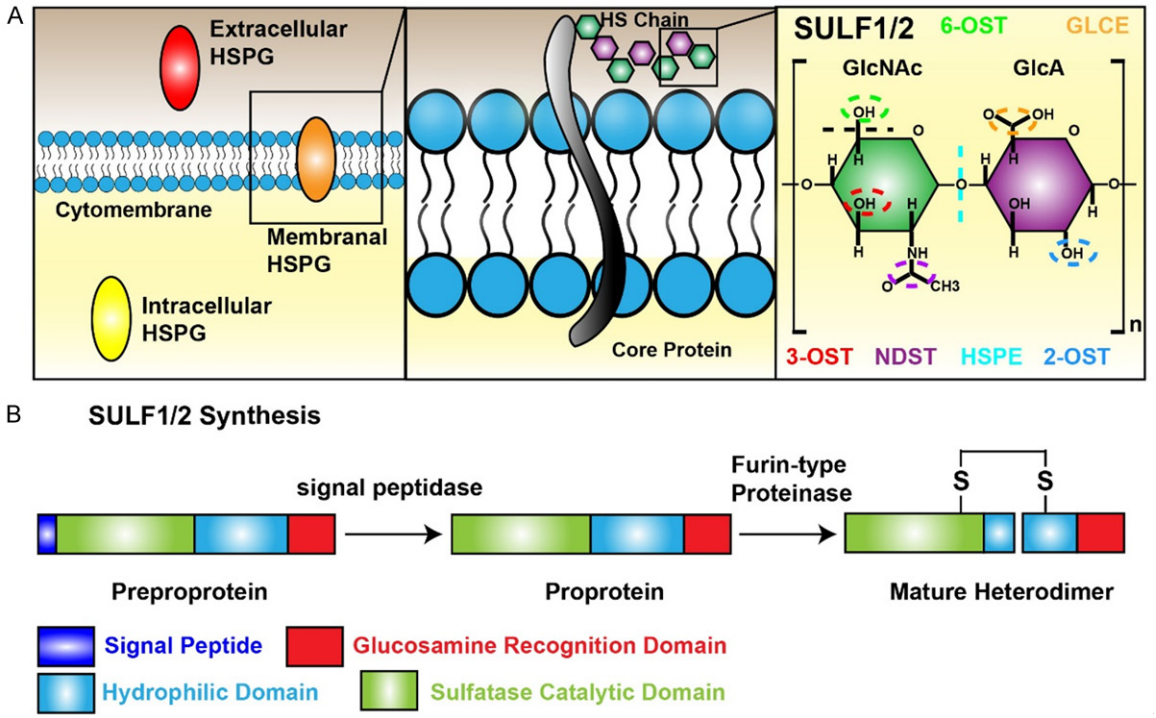

Figure 1. The structure and function of HSPGs and SULFs. A. HSPGs are divided into extracellular, membranal and intracellular subtypes according to their cellular location. HSPGs are composed of the core proteins and HS chains. After biogenesis HSPGs undergo a series of modifications, among them SULFs catalyze hydrolysis of 6-O sulfates. B. The biogenesis of SULFs. SULFs are synthesized as preproproteins. After removal of the signal peptide, SULFs are cleaved by the furin-type proteinase and the fragments are joined by disulfide bonds. GlcA: glucuronic acid, GlcNAc: N-acetyl glucosamine, 2-OST: 2-sulfotransferase, 3-OST: 3-sulfotransferase, 6-OST: 6-sulfotransferase, NDST: N-deacetylase/N-sulfotransferase, GLCE: glucuronic acid epimerase, HPSE: heparinase.

SULF1 in tumorigenesis and tumor progression seems inconsistent. In ovarian cancers and breast cancers, SULF1 can inhibit tumor progression and reduce chemoresistance of cisplatin, while the overexpression of SULF1 in colorectal cancer (CRC) and pancreatic cancer is usually connected with advanced stages and poor prognosis [48-51].

Specific mechanisms of SULFs in tumor metastasis

The roles of SULF1 and SULF2 in tumor metastasis exhibit variability across different types of cancers. Previous studies have demonstrated the pro-metastasis roles of SULF2 in most cancers, while the functions of SULF1 vary according to types of cancers [47, 52]. Therefore, SULFs may regulate tumor metastasis via different molecular mechanisms. Desulfation of HSPGs is the essential mechanism of SULFs in regulating metastasis. Based on this mechanism, SULFs can influence the reprogramming of tumor microenvironment (TME) and epithelial mesenchymal transition (EMT) process in metastasis. Moreover, epigenetic modifications of SULF1 and SULF2 play critical roles.

SULFs regulate tumor metastasis by HSPGs associated pathways

The 6-O sulfation of HS chains has been proved to regulate the binding of HSPGs to ligands and receptors, which influence metastasis pathways either directly or indirectly [53]. SULFs mainly regulate HSPGs associated pathways through different methods. On the one hand, 6-O sulfated HS chains are common storage sites for many bio-active ligands, and SULFs can facilitate the release of these ligands. On the other hand, SULFs may influence the co-receptor complexes formation and regulate the downstream signaling [38, 54, 55]. In this text, these mechanisms of SULFs are discussed according to HSPGs associated signaling pathways in tumor metastasis, such

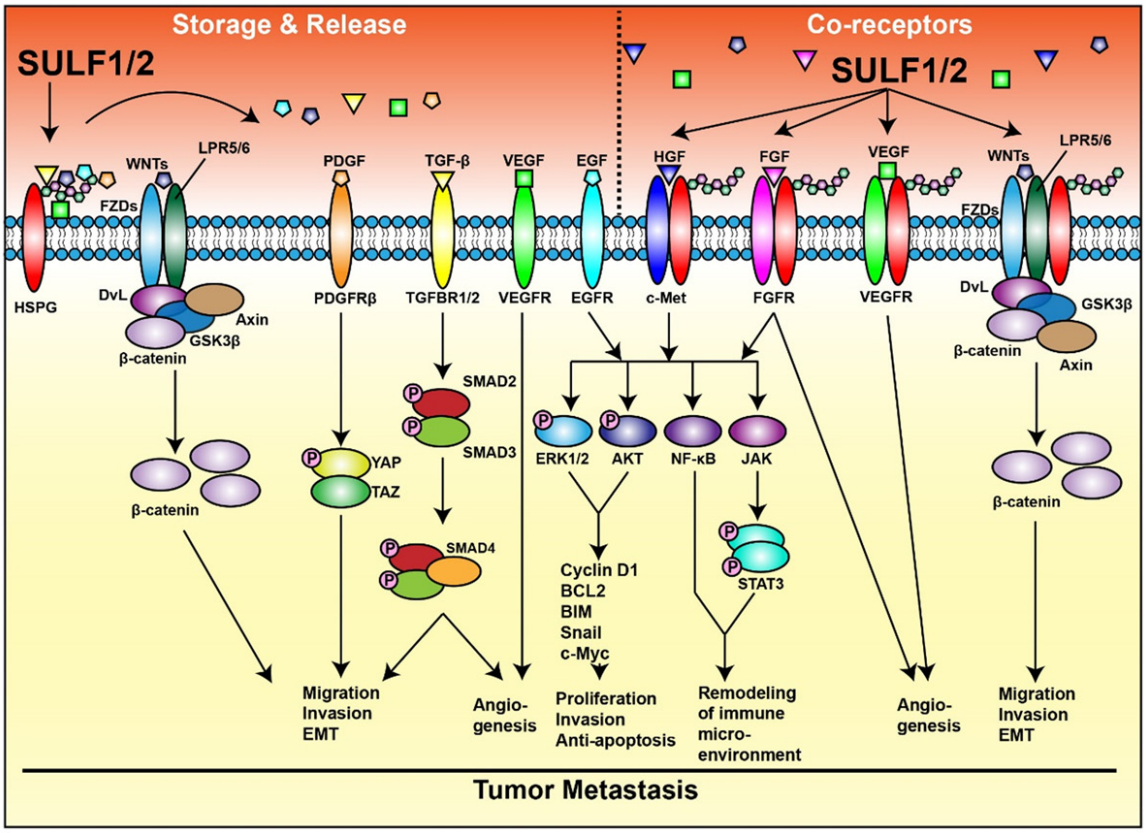

Figure 2. Specific mechanisms of SULFs in tumor metastasis. SULFs mainly regulate tumor metastasis through influencing the HS-related signaling pathways. For each, the modifications of HS-chains by SULFs can affect the release of bio-active ligands or the formation of co-receptor complex. Various pathways are involved in and regulate the metastasis associated processes including proliferation, migration, invasion, EMT, angiogenesis and TME remodeling.

as WNT/β-catenin, TGF-β/SMAD, FGF and other HS-binding growth factors (GFs). Moreover, some downstream pathways indirectly regulated by SULFs are involved as well (**Figure 2**).

WNT/β-catenin

WNT refers to a cluster of secreted glycoproteins. Up to now, researchers have identified 19 WNT ligands, which serve diverse functions in regulation of different pathways [56]. Among them, WNT1, WNT3A and WNT8 activate the canonical WNT pathway by binding to frizzled and lipoprotein receptor 5/6, subsequently triggering the nuclear functions of β-catenin. Meanwhile, WNT5 and WNT11 activate small GTPases and the protein kinase JNK, which is the non-canonical pathway. Both pathways play important roles in tumor initiation and progression [57, 58]. HSPGs function as co-receptors and storage sites of WNT ligands, while SULFs predominantly influence the canonical WNT/β-catenin pathway in tumor metastasis [59]. In gastric cancer, SULF1 inhibits cell invasion by downregulating β-catenin and downstream Cyclin D1 and c-Myc [60]. Moreover, studies in prostate cancer reported that SULF1 could reduce WNT3a-driven bone metastasis [61]. As for SULF2, most recent researches proved pro-metastasis function of SULF2 by activating WNT/β-catenin pathway. In CRC, both SULF1 and SULF2 were reported to alter HS chains substitution pattern, thereby increase the accumulation of active β-catenin and induce invasiveness of cancer cells [62]. In another example, SULF2 was reported to form a ternary complex with WNT3A and transmembrane HSPG glypican 3 (GPC3). Then the desulfation of GPC3 by SULF2 enhanced the release of WNT proteins, promoting their binding with Frizzled receptors [63]. Roughly, SULF2 is recognized for promoting tumor metastasis by activating WNT signaling pathway, while the role of SULF1 alters in different cancers.

TGF-β/SMAD

TGF-β is a multifunctional cytokine which plays crucial roles in malignant evolution of cancer cells [64]. TGF-β can bind to type II receptor, attribute to phosphorylation of type I receptor and SMADs, then activate downstream genes [65]. The TGF-β signaling pathway can modulate tumorigenesis, cell invasion and microenvironment modification in diverse cancers [66]. SULFs mainly regulate TGF-β signaling pathway by desulfating HS chains, thereby enhancing the release of TGF-β. SULF1 has been found upregulated in HCC and is associated with poor prognosis [67]. Renumathy Dhanasekaran et al. found that SULF1 could inhibit the interaction of TGFβ1 and its sequestration receptor TGFBR3. Consequently, overexpression of SULF1 could promote TGFβ1 secretion and lead to activation of downstream signaling, then enhance HCC cells migration and invasion [68, 69]. Likewise, SULF2 can induce TGF-β signaling in similar methods. In pancreatic ductal adenocarcinoma (PDAC), SULF2 induces the TGF-β/SMAD pathway by regulating GDF15, a member of the TGF-β superfamily [70]. The activation of TGF-β/SMAD pathway by SULF2 was also reported in lung cancers, which contributed to invasiveness of tumor cells [44, 71]. In conclusion, TGF-β signaling is a key player in tumor metastasis, and SULFs exhibit similar functions of activating TGF-β signaling via HSPG-mediated methods, thereby promoting tumor metastasis in vitro and in vivo.

FGF

The fibroblast growth factors (FGF) and their corresponding receptors play critical roles in various biological processes, especially differentiation, proliferation and tumorigenesis [72, 73]. FGFs bind to and dimerize cognate receptors, then interact with HSPGs and establish stable ligand/receptor complexes [74]. The desulfation of HS chains by SULFs may influence the functions of HSPGs and accordingly regulate FGF signaling pathway [75]. Recent studies proved the distinct modifications of HS chains mediated by SULF1 and SULF2 [42, 76]. Generally, SULF1 is regarded as an inhibitor for FGF signaling. In breast cancers, it was reported that transcriptional silence of SULF1 under hypoxia could enhance FGFR2 phosphorylation, thereby facilitating cell migration and invasion [77]. Similarly, researches in head and neck squamous carcinoma (HNSC) also showed that SULF1 could inhibit tumor metastasis by downregulating FGF signaling [78]. In contrast, SULF2 was reported to exert different functions. Further exploration in HCC by Lai JP et al. revealed that SULF2 could promote FGF signaling by upregulating GPC3, leading to increased FGF2 binding and inducing tumor growth and metastasis [79]. Previous experiments have concluded the distinct function of SULF1 and SULF2 in modulating the FGF signaling pathway.

Other HS-binding GFs signaling pathways

Apart from the signaling pathways mentioned above, other HS-binding growth factors can be modulated by SULFs as well. EGFR is the transmembrane receptor for various ligands including epidermal growth factor (EGF), heparin-binding EGF (HB-EGF), transforming growth factor α (TGF-α) and amphiregulin (AR) [80]. SULF1-mediated desulfation of cell surface HSPGs has been implicated in the reduction of EGFR phosphorylation, leading to the inhibition of tumor metastasis [81, 82]. In contrast, SULF2 could increase the release of EGFR ligands and induce the downstream pathways. Recent researches in HCC found that SULF2 stimulated EGFR signaling and facilitated lipocalin 2 transcription, thereby induced tumor progression [83]. Another set of growth factors, hepatocyte growth factors (HGFs), and their receptor c-Met are linked to tumorigenesis and metastasis [84]. As shown in previous work, SULF1 was regarded as a suppressor of HGF signaling, which consequently promoted apoptosis of HCC cells [85]. Researches also revealed that downregulation of SULF1 by EZH2 could facilitate phosphorylation of c-Met and activation of downstream signaling in chondrosarcomas [86]. PDGFs are firstly identified in active platelet and belong to HS-binding GFs family [87]. They can bind to PDGF receptors and promote their dimerization and phosphorylation, thereby regulate various downstream pathways and promote cancer progression and metastasis [88]. Recent researches reported that SULF2 knockdown in glioblastoma caused remarkable decrease of PDGFRα activation, and overexpression of SULF2 in cholangiocarcinoma induced PDGFRβ and downstream YAP signaling activation [45, 89]. Additionally, dys-

regulation of SULFs in many cancer types can impact VEGFs, thereby modulating angiogenesis - an integral process in metastasis [90, 91].

Indirectly activated signaling pathways

In addition to binding with heparan sulfate (HS) growth factors, SULFs play a pivotal role in indirectly regulating numerous classical signaling molecules and pathways associated with tumors, exerting either pro- or anti-metastatic functions. Predominantly implicated pathways include MAPK and PI3k/AKT. As formerly published, experiments in lung cancer and ovarian cancer cells demonstrated that loss of SULF1 could induce tumorigenesis and metastasis via activating phosphorylation of ERK and AKT [92, 93]. Additionally, in malignant mesothelioma, overexpression of Syndecan-1 could impede the release of SULF1, consequently stabilizing heparan sulfate (HS) chains and activating the MAPK pathway [94]. Conversely, SULF2 was reported to activate the MAPK and AKT pathways in several kinds of cancers [95, 96]. Signal transducer and activator of transcription 3 (STAT3) plays significant roles in cell proliferation, differentiation, metabolism and malignant characteristic [97, 98]. Canonical STAT3 signaling is initiated by Janus kinase (JAK), while the non-canonical pathway exhibit crosstalk with MAPK or AKT signaling [99]. Researchers found that exogenous SULF1 in breast cancer could inhibit STAT3 phosphorylation in non-canonical signaling pathway independent of JAK2, then induce cell cycle arrest and inhibit cell migration and invasion [100]. Contrastingly, recent studies have reported that SULF2 influences the canonical JAK/STAT3 signaling. For example, SULF2 could induce HCC growth and migration by upregulating GLI1 and transcriptionally activating JAK/STAT3 signaling [101]. Furthermore, the overexpression of SULF2 induced by radiotherapy could induce interleukin-6 secretion, then increase STAT3 phosphorylation and mediate malignant effects [102, 103]. Moreover, NF-κB, the critical transcription factor in immune and inflammation responses could be promoted by SULF2 [104]. SULF2 could activate NF-κB signaling and stimulate the secretion of inflammatory cytokines in HCC by upregulating GPC3 [105]. These results have illuminated the functions of SULFs in indirectly regulating various metastasis signaling pathways.

SULFs regulate tumor metastasis by reprogramming TME

Tumor microenvironment (TME) is constituted by not only malignant cells, but also the fibroblasts, stromal cells, immune cells and vasculature, which exert different functions in tumor initiation and progression [106, 107]. Reprogramming of the TME mainly influences the metastasis process in 3 different ways including angiogenesis, ECM reorganization and immune response alteration [108-110]. Recent studies have focused on the roles of SULFs in TME reprogramming. Firstly, as HSPGs participate in composition of ECM, SULFs serve as important ECM-related molecular capable of modulating ECM reorganization. SULF1 was identified as a hub ECM gene in bladder cancers and gastric cancers, potentially influencing the maintenance of tissue homeostasis and patient prognosis [111, 112]. Immuno-histochemistry (IHC) assays in cancer tissues showed high expression of SULF1 in stromal cells, which could independently predict lymph node metastasis [113]. SULF2 is also related to ECM remodeling. For example, the cancer associated fibroblasts of HCC could release stromal SULF2 into ECM, which could influence the modification of GPC3 in ECM and promote HCC metastasis by activating downstream molecules like β-catenin, STAT3 and NF-κB [114]. Furthermore, researchers indicated that high expression of SULF2 in hepatic stellate cells could increase the levels of collagen I and α-SMA, thereby promoting liver fibrosis, which is an important risk factor for HCC [115]. Secondly, SULFs could modulate tumor angiogenesis in the metastasis process, mainly through VEGF signaling pathway. Researchers found that loss of SULF1 in several types of cancers could facilitate phosphorylation of VEGFR2 and promote angiogenesis [116]. And investigations in human umbilical vein endothelial cells (HUVEC) indicated that silence of SULF1 could promote cell proliferation under stimulation of VEGF, FGF2 and HGF [90]. However, SULF2 were suggested to promote angiogenesis in vitro and in vivo. On the one hand, overexpression of SULF2 by the telomeric protein TRF2 in the vasculature of many cancer types could induce VEGF-A release, then promote HUVEC cells differentiation and tubule-formation [91]. On the other hand, studies in endothelial tip cells indicated that SULF2 could

upregulate VEGFR2 and the co-receptor NRP, thereby facilitate VEGFA-induced sprouting angiogenesis [117]. Moreover, SULF1 and SULF2 were reported as immune regulators, stimulating macrophage phagocytosis and antigen presentation in response of proinflammatory stimuli and inflammation [118]. In bladder cancers, researchers also demonstrated that SULF2 could promote M2 polarization of macrophage via increasing IL-8 release and activating JAK/STAT3 signaling [119]. SULF1 was upregulated in gastric cancers and positive related to CD8+ T cells, CD4+ T cells and macrophage infiltration [120]. Further investigations in the mechanisms of how SULFs regulate immune response and tumor progression are needed.

SULFs regulate tumor metastasis by affecting EMT process

EMT is an essential biological procedure in which cells lose epithelial characteristics (e.g., cell polarity and adhesion) and transform into mesenchymal phenotypes [121, 122]. The EMT process encompasses diverse morphological and functional alterations of related cells, along with downregulation of epithelial markers like E-cadherin and upregulation of mesenchymal markers such as N-cadherin and vimentin [123]. EMT significantly augments the aggressive behavior of tumor cells, facilitating their invasion of adjacent or distant tissues and thereby contributing to tumor metastasis [124, 125]. In the prevailing view, SULF1 and SULF2 exerted different functions in EMT process. Traditionally identified as an EMT inhibitor, SULF1 was shown in recent studies to suppress hepatocellular carcinoma (HCC) cell EMT by inhibiting the MAPK and AKT pathways [126]. Moreover, Mahmoud et al. made further exploration of SULF1 in HCC by constructing overexpressed and knockdown murine HCC cell lines. Their findings revealed that SULF1 could attenuate HCC cells EMT by downregulating mesothelin, thus inhibit cells growth and invasion in vitro and in vivo [127, 128]. In contrast, SULF2 was reported to upregulate SNAI1 and vimentin to promote EMT in HCC [129]. Additionally, researches in breast cancer showed SULF2 could promote activity of MMP9, and overexpression of SULF2 in prostate cancer contributed to upregulation of mesenchymal markers CD44, N-cadherin and vimentin [130, 131]. In conclusion, SULF1 and SULF2 play different roles in EMT regulation, which is an important process in tumor metastasis.

Epigenetic modification of SULFs modulate tumor metastasis

Besides regulating HS-related pathways, tumor microenvironment and EMT process, different types of epigenetic modification in SULFs can also influence the metastasis process in several cancers. Alternative splicing (AS) is one kind of critical post-transcriptional modification which produces diverse mRNA transcripts by differential ligation of 3' and 5' end in exons [132, 133]. During recent decades, several different AS of SULFs were discovered and reported in metastasis process. For instance, researchers isolated two different AS of SULF1 which were named as SULF1A and SULF1B. Further investigation showed that SULF1A and SULF1B exerted opposing functional activities in regulating angiogenesis and WNT signaling [134]. And the first effective tumor-specific SULF2 AS was found in lung tumor samples, which could induce HGF and MAPK signaling [135]. More recent studies verified the expression of various short AS variants of SULF1 and SULF2 in PDAC and breast cancers. In PDAC, the expression of SULF1/SULF2 variants showed distinctions in different regions and different stages in PDAC progression. Specifically, SULF1 variants were consistently expressed in epithelial acinar cells, while SULF2 variants mainly located in stromal cells. Both variants could reduce the facilitation of cell growth by SULF1 and SULF2. In breast cancers, researchers showed that SULFs short AS contributed to lymphatic metastasis [136-138]. Epigenetic silencing of SULFs were also reported in many types of cancers. In ovarian cancers, researchers demonstrated that the overexpression of variant hepatic nuclear factor 1 (vHNF1) inhibited SULF1 transcription via binding to its promoter, which also contributed to cisplatin resistance [139]. The demethylating agent 5'-aza-2'-deoxycytidine could reverse the epigenetic silencing of SULF1 and restore sensitivity to chemotherapy [48]. Similarly, Tessema et al. also showed the methylation silencing of SULF2. SULF2 methylation could inhibit tumor metastasis and sensitize tumor cells to topoisomerase-1 inhibitors, thereby improve the overall survival [140]. These results had dem-

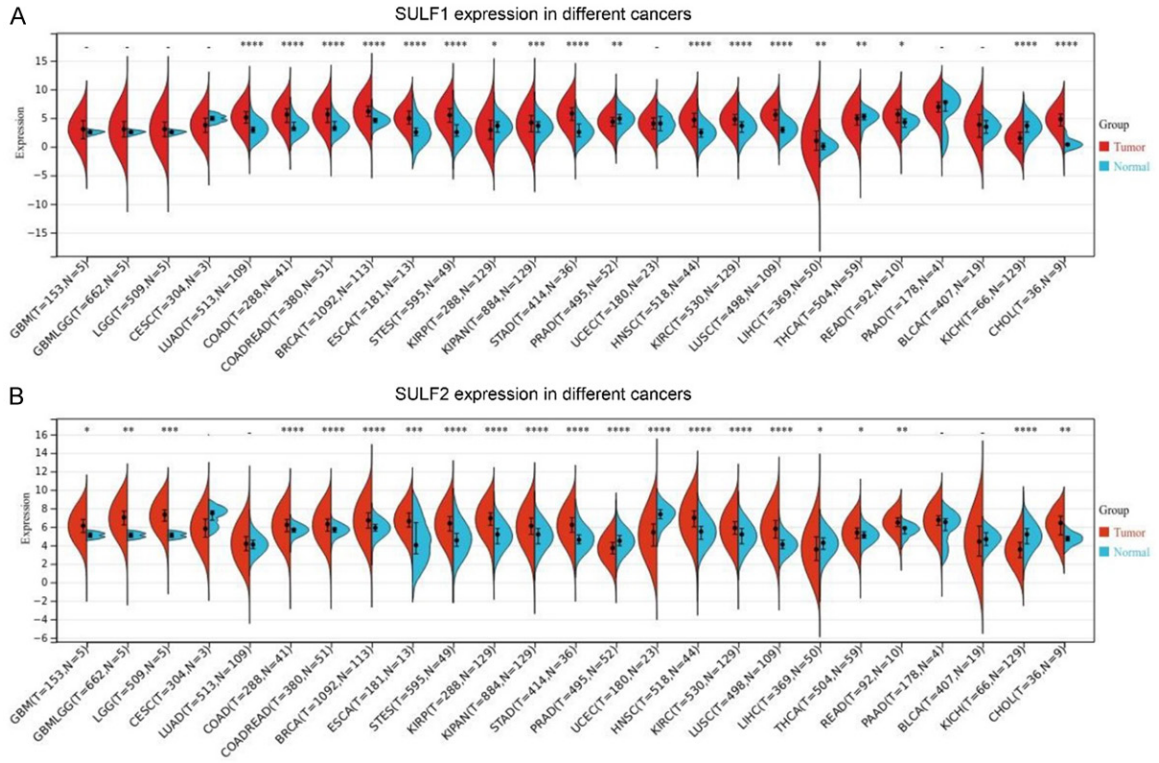

Figure 3. The expression of SULFs in different types of cancers. A, B. SULF1 and SULF2 have similar structure and desulfation function, but their expression varies in different cancers. The results were analyzed in TCGA database. GBMLGG: glioblastoma and low-grade glioma, GBM: glioblastoma multiforme, LGG: low-grade glioma, CESC: cervical squamous cell carcinoma, LUAD: lung adenocarcinoma, COAD: colon adenocarcinoma, COADREAD: colon adenocarcinoma and rectum adenocarcinoma, BRCA: breast invasive carcinoma, ESCA: Esophageal carcinoma, STES: stomach and esophageal carcinoma, KICH: kidney chromophobe, KIRP: kidney renal papillary cell carcinoma, KIRC: kidney renal clear cell carcinoma, KIPAN: pan-kidney cohort, STAD: stomach adenocarcinoma, PRAD: prostate adenocarcinoma, UCEC: uterine corpus endometrial carcinoma, HNSC: head and neck squamous cell carcinoma, LUSC: lung squamous cell carcinoma, LIHC: liver hepatocellular carcinoma, THCA: thyroid carcinoma, PAAD: pancreatic adenocarcinoma, BLCA: bladder urothelial carcinoma, CHOL: cholangiocarcinoma.

onstrated the epigenetic modifications of SULFs could impact tumor metastasis and tolerance to chemotherapeutics.

Distinct functions of SULFs in metastasis of different types of cancers

SULFs can regulate tumor metastasis through different mechanisms. Although SULF1 and SULF2 obtain similar molecular structure and exert analogous desulfation functions toward HS chains, their biological behaviors vary from different types of cancers. We analyzed the expression of both SULF1 and SULF2 in TCGA database and the results were showed in **Figure 3**. In our review, the concrete roles of SULFs in different types of cancers are summarized, which can facilitate researchers to realize the relationship between SULFs and tumor metastasis. The detailed information is concluded in **Table 1**.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most prevalent form of liver cancer, which ranks the third leading cause of cancer-associated mortality [141]. Previous evidence uncovered the abnormal expression of SULFs in HCC. In the prevailing view, SULF1 was defined as a tumor-suppressor in HCC. Lai et al. reported the methylation silencing and loss of heterozygosity (LOH) in SULF1, which downregulated SULF1 and facilitated tumor growth and inhibited chemotherapy apoptosis [85, 142]. The anti-metastasis role of SULF1 was also demonstrated though suppression of AKT and MAPK signaling [126]. However, further studies in some

Table 1. The functions of SULFs in different types of cancers

Cancer type	Functional SULFs	Specific functions in metastasis	Molecular mechanisms and related pathways	Ref.
HCC	SULF1	Downregulated by LOH and methylation silencing	Influence of epigenetic modification	[85, 142]
		Suppress proliferation, invasion and EMT, inhibit lymphatic metastasis	Attenuate AKT and MAPK pathways	[126, 128, 164]
		Promote migration, invasion and EMT	Activate HS-related TGF-β/SMAD pathway	[68]
	SULF2	Increase macrophage migration and recruitment, promote EMT process	Activate NF-κB and STAT3 pathways, remodel TME	[114, 129]
		Promote proliferation, migration and invasion	Promote proliferation, migration and invasion	[63, 79]
		Promote angiogenesis and liver fibrosis	Activate HS-related TGF-β/SMAD pathway, remodel TME	[115, 143]
Breast Cancer	SULF1	Downregulated by LOH and methylation silencing	Influence of epigenetic modification	[145]
		Suppress proliferation, migration and invasion, induce cell cycle arrest and apoptosis	Attenuate HS-related FGF, HGF, and downstream AKT, MAPK, STAT3 pathways	[52, 77, 100]
		Inhibit angiogenesis	Attenuate HS-related FGF and VEGF pathways, remodel TME	[90]
	SULF2	Promote angiogenesis and lymph angiogenesis	Activate HS-related VEGF pathway, remodel TME	[146, 165]
		Transform DCIS into invasive ductal carcinoma	Not mentioned	[131]
CRC	SULF1	Overexpress in advanced and metastatic CRC, associate with poor prognosis	Not mentioned	[50, 166]
		Promote proliferation and invasion	Activate HS-related FGF and WNT pathways	[62, 149]
	SULF2	Promote angiogenesis	Activate HS-related VEGF pathway, remodel TME	[91]
		Serve as biomarkers of microenvironment and invasion	Not mentioned	[149-151]
		Promote proliferation, migration and invasion	Activate HS-related WNT and downstream MAPK, AKT pathways	[62, 96]
NSCLC	SULF1	Suppress proliferation and tumorigenesis in previous views Upregulated in NSCLC tissues by broader analyses	Modulate AKT and MAPK pathways	[93, 153, 154]
	SULF2	Promote γ-Irradiation-Induced metastasis	Not mentioned	[167]
		Inhibit metastasis while methylated silenced	Influence of epigenetic modification	[140]
		Promote migration, invasion and EMT	Activate HS-related WNT and TGF-β/SMAD pathways	[44, 155]
Ovarian Cancer	SULF1	Downregulated by LOH and methylation silencing	Influence of epigenetic modification	[48, 139]
		Reduce micro vessel density and inhibit angiogenesis	Attenuate HS-related FGF and VEGF pathways, remodel TME	[90, 116]
		Suppress proliferation and invasion, induce cell apoptosis	Attenuate AKT and MAPK pathways	[92]
GBM	SULF2	Overexpressed in mesenchymal and pro-neural subtypes GBM	Positively correlate with PDGFRA expression	[160, 163]
		Promote proliferation, migration, and invasion	Activate HS-related PDGF pathway	[89]
Prostate Cancer	SULF2	Promote migration, invasion and EMT	Activate HS-related WNT pathway	[130]
Bladder Cancer	SULF2	Promote polarization of M2 macrophages	Activate IL8/STAT3 pathway, remodel TME	[119]
		Serve as diagnostic and prognostic marker, promote lymph node metastasis	Not mentioned	[168]

SULF1 and SULF2 have been reported to influence tumor metastasis of HCC, breast cancers, NSCLC, CRC, ovarian cancers, GBM, prostate cancers and bladder cancers. The specific mechanisms are showed above.

HCC revealed that high expression of SULF1 was associated with poor prognosis, and SULF1 could increase TGFβ releasing and promote invasion and EMT [68]. Unlike the controversial function of SULF1 in HCC, SULF2 was proved as an oncogenic factor. It was demonstrated that overexpression of SULF2 could stimulate HCC cells migration, invasion and EMT by activating HS-related TGF-β, FGF, WNT signaling, as well as TME reorganization [19, 63, 79, 143]. In summary, both SULFs participate in HS-related pathways and TME regulation, but the specific role of SULF1 in HCC need further investigation.

Breast cancer

Breast cancer remains the foremost contributor to both cancer incidence and mortality among women [144]. Different effects of SULFs have been reported in breast cancer. SULF1 is downregulated in breast cancer cells and tissue samples, which is correlated with high methylation of 5' promoter region [145]. SULF1 can influence numerous processes in metastasis of breast cancer such as migration, invasion, EMT, angiogenesis and induce cell cycle arrest and apoptosis [77, 100]. These effects are mainly associated with the modulation of HS-related pathways. In contrast, SULF2 is usually regarded as a promoter of metastasis in breast cancer. Ashwani Khurana et al. provide substantiation that SULF2 could prompt the transition from ductal carcinoma in situ (DCIS) to more invasive ductal carcinoma [131]. Further studies also showed significant effect on HS-related pathways mediated by SULF2 [146, 147]. With the recent advances, SULF1 and SULF2 exhibit contrasting functions in breast cancer while modulate similar signaling pathways.

Colorectal cancer

Researches in CRC showed consistent oncogenic functions of SULF1 and SULF2 [47, 148]. SULFs were considered promising invasion-related biomarkers. Anastasia et al. demonstrated that SULFs could be defined as potential microenvironment factors in CRC, while the augmented cell migration activity was also proved through exogenous SULF1 and SULF2 [62, 149]. More recent gene analysis showed that SULF2 upregulation might account for local invasion of CRC [150]. In addition, SULF2 was regarded as one of microsatellite instability (MSI) biomarkers, whose identification could reflect assessment of therapy stratification and overall survival [151].

Non-small cell lung cancer

Lung cancer is the most common type of cancer and the leading cause of cancer-associated morality. Non-small cell lung cancer (NSCLC) represents about 80-85 percent of lung cancers [152]. In the past debates, SULF1 was identified as an inhibitor of MAPK and AKT signaling, thereby suppressed tumor progression and metastasis [93]. However, more recent studies showed that NSCLC tissues expressed higher level of SULF1 compared with nonmalignant adjacent tissues [153]. Overexpression of SULF1 could facilitate migration and invasion of NSCLC cells [154]. SULF2 were defined as an oncogene for NSCLC. Previously investigations revealed that SULF2 could promote tumor metastasis through activating TGF-β/SMAD and WNT signaling pathways [44, 155]. In a word, the current view is that SULFs are consistently served as promoter of NSCLC.

Ovarian cancer

Ovarian cancer is the fourth most common cancer of female worldwide [156]. Abundant of researches have showed that SULF1 is a known suppressor in ovarian cancers [157]. The role of inhibiting metastasis by SULF1 is reflected through several aspects. Firstly, the loss of SULF1 in ovarian cancer is caused by LOH and epigenetic silencing, as well as upregulation of suppressive transcription factor vHNF [48, 139]. Secondly, SULF1 participate in remodeling of microenvironment through inhibiting angiogenesis [90, 116]. Thirdly, SULF1 regulate metastasis process via HS-related GF signaling [54, 92]. Moreover, researchers also found that single nucleotide polymorphisms (SNPs) of SULF1 could alter the aggressiveness and prognosis of ovarian cancers [158]. However, there were few studies about SULF2 in ovarian cancer, which still need more investigation to explore the specific mechanisms.

Glioblastoma multiforme

Glioblastoma multiforme (GBM) represents about 80% of the malignant brain tumors in adults [159]. The dysregulation of HS-related

GF and RTK signaling plays a pivotal role in facilitating the invasive properties of GBM cells within neighboring brain tissues [160, 161]. Therefore, SULFs have been regarded as crucial regulator in GBM. Previous studies showed that expression of SULF1 and SULF2 depended on different GBM subtype [162]. For example, SULF1 was downregulated in classical and neural GBM, related to amplification of EGFR. Meanwhile, enrichment expression of SULF2 in mesenchymal and pro-neural GBM was associated with abnormal PDGFRα stimulation [160, 163]. Phillips et al. verified the decreased PDGFRα activation in SULF2 knock-out mice, and SULF2 mainly regulated HS-related pathways in pro-neural type of GBM [89]. In brief, SULFs exhibit different expression in different subtypes of GBM, and affect GBM development and metastasis together.

SULFs are promising targets of adjuvant therapy in metastatic cancers

Except for surgery resection, adjuvant therapy also plays critical roles in the treatment of malignant solid tumors [169]. Adjuvant treatments consist of chemotherapy, radiotherapy, immunotherapy, etc. [170]. However, the efficacies of these therapeutics are still limited by adverse effect, drug susceptibility and tolerance. In recent evidence, more and more studies paid attention to roles of SULFs in neoadjuvant therapy. Firstly, SULFs regulate adverse effects of adjuvant therapies, particularly in radiotherapy. γ-irradiation is the most common used ionizing radiation method. However, it may induce invasion of cancer cells, posing a major challenge for radiotherapy. Interestingly, Jung et al. revealed that γ-irradiation-induced invasion were mediated by SULF2. Their findings showed that the transcriptional upregulation of SULF2 induced by ionizing radiation could promote the invasiveness of cancer cells via STAT3 and β-catenin pathways [102, 171]. Further investigation suggested that dendrobine could inhibit ionizing radiation-induced invasion through suppressing SULF2 expression and ionizing radiation-induced signaling [167]. Secondly, SULFs could impact the therapeutic sensitivity of drugs or radiotherapy, which is a promising target for combination therapy. It was reported that high expression of SULF1 could enhance the efficacy of Palbociclib, a CDK4/6 inhibitor, in inducing cell cycle arrest and apoptosis, thus inhibiting proliferation, EMT and invasion in triple-negative breast cancer [100]. In HCC, researchers reconstructed radiation-inducible oncolytic adenovirus overexpressing SULF1 and transferred them into HCC cells. The over-expression of SULF1 induced by I131 radiation could enhance cellular sensitivity to radioimmunotherapy [172]. Moreover, the deactivation of SULF2 via mutation or inhibitors exhibited an increased susceptibility of liver cancer to sorafenib [83]. Thirdly, SULFs mediated chemotherapy resistance in many types of cancers. For example, cisplatin is a common antitumor drug which is widely applied in lung cancer, ovarian cancer, prostate cancer, HNSC and malignant lymphoma. Many previous studies showed loss of SULF1 in HCC, malignant mesothelioma, HNSC and especially ovarian cancer contributed to cisplatin resistance [78, 85, 173-175]. In contrast, artificially knocking down SULF2 could decrease cisplatin resistance in cholangiocarcinoma, and monoclonal antibody targeting SULF2 could inhibit cholangiocarcinoma progression [45]. OKN-007, one enzymatic activity inhibitor of SULF2, could suppress tumor growth and metastasis in HCC and GBM [176, 177]. The combination therapy value of OKN-007 with other drugs were also validated in HCC and GBM [83, 178, 179]. Collectively, these findings underscore the significant role of SULFs in influencing adjuvant therapy and present promising novel targets for therapy.

Conclusion and prospect

Tumor metastasis constitute a complex multistep biological process characterized by the dysregulation of pivotal molecules and signaling pathways, remaining the predominant cause of mortality in malignant solid tumors. This review predominantly centers on elucidating the role of SULFs in modulating tumor metastasis. SULF1 and SULF2 contain similar regions which can selectively cut out 6-O-sulfate group from HS chains of HSPGs. For this reason, modification of HSPGs by SULFs accounts for the primary mechanism of SULFs in modulating metastasis process.

Recent researches have showed that SULF2 appears to promote tumor progression and metastasis, but the function of SULF1 is still controversial. In the majority of cancers, SULF1

act as an inhibitor to tumor progression and metastasis. However, conflicting studies indicate a pro-metastasis role of SULF1 in specific cases of HCCs, CRCs, and NSCLCs. This suggests that SULF1 may exert varied effects on tumor metastasis within certain cancer contexts.

Researchers dedicated significant attention to the intricate interplay between cancer cells and their microenvironment in the quest for cancer therapy. SULFs play a crucial role in modifying HSPGs within the tumor microenvironment, impacting the availability of exogenous ligands. Targeting SULFs show a noteworthy reduction in adverse effects and drug resistance, accompanied by an enhancement in therapeutic sensitivity. Except for previously reported adenovirus, inhibitor or antibodies, we advocate for the exploration of genetic and biological methods to target SULFs. Advanced nanomedicine systems, such as liposomes, supramolecules, dendrimers, in conjunction with aptamers, offer promising avenues for delivering small-molecule inhibitors or gene segments to target SULFs within cancer cells. And the RNA therapeutics targeting SULFs, including small interfering RNAs (siRNA), microRNAs (miRNA), antisense oligonucleotides (ASOs), can be enveloped into the nanomedicine system [180, 181]. Given the direct or indirect regulation of numerous signaling pathways by SULFs, we propose potential synergistic effects by combining signaling inhibitors with SULFs-targeted therapeutics. In conclusion, we summarized the roles of SULFs in tumor metastasis, and elucidated the potential application of targeting SULFs in tumor adjuvant therapy.

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Disclosure of conflict of interest

None.

Abbreviations

SULFs, 6-O-endosulfatases; SULF1, sulfatase 1; SULF2, sulfatase 2; HSPG, heparan sulfate proteoglycans; ECM, extracellular matrix; TME, tumor microenvironment; TGF-β, Transforming growth factor-β; EMT, epithelial mesenchymal transition; FGF, fibroblast growth factors; VEGF, vascular endothelial growth factor; AS, Alternative splicing; STAT3, Signal transducer and activator of transcription 3; HCC, Hepatocellular carcinoma; CRC, colorectal cancer; GBM, Glioblastoma multiforme.

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