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REVIEW

Insights into the molecular roles of heparan sulfate proteoglycans (HSPGs—syndecans) in autocrine and paracrine growth factor signaling in the pathogenesis of Hodgkin's lymphoma

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Abstract Syndecans (SDC, SYND) comprise a group of four structurally related type 1 transmembrane heparan sulfate proteoglycans (HSPGs) that play important roles in tumorigenic processes. SDCs exert signaling via their protein cores and their conserved transmembrane and cytoplasmic domains or by forming complexes with growth factors (GFs). In classical Hodgkin's lymphoma (cHL), a lymphoid neoplasm of predominantly B cell origin, SDC1 and SDC4 are the active SDCs, and a number of GF (vascular endothelial growth factor, fibroblast growth factor, etc.) signaling pathways have been studied. However, despite extensive pre-clinical and clinical research on SDC-mediated GF signaling in many cancer types, there is very limited data for this interaction in cHL. Thus, this review highlights the relevant literature focusing on the potential interactions of SDCs and GFs in cHL pathogenesis. Also discussed are the pre-clinical and clinical studies targeting signaling through these pathways.

Keywords Syndecan-1 · CD138 · Growth factors · Hodgkin's lymphoma · Cancer · Autocrine · Paracrine · Heparan sulfate proteoglycans

Introduction

The syndecans (SDC, SYND) comprise a family of highly conserved type I transmembrane proteins that are present on the surface of adherent cells and cells of the hematological system. In humans, there are four members, designated SDC1, SDC2, SDC3, which are tissue-specific, and SDC4, which is cell type-specific [1]. Each of these heparan sulfate proteoglycans (HSPGs) consists of an extracellular domain (ectodomain) carrying glycosaminoglycan (GAG) side chains, a transmembrane domain and a short cytoplasmic domain [2]. SDCs have been implicated in a wide range of cellular processes including differentiation, cell adhesion [3, 4], cytoskeletal organization, cell spreading and migration [5–7], infiltration, and angiogenesis [8, 9]. These processes are partly facilitated by the interaction of the heparan sulfate (HS) chains of SDCs, with other factors, including heparin-binding growth factors (GFs) such as fibroblast growth factors (FGFs), vascular endothelial growth factors (VEGFs), transforming growth factor-β (TGF-β), platelet-derived growth factors (PDGFs), and cytokines. These interactions play important roles in cancer development and progression [10]. In the tumor microenvironment (TM) of classical Hodgkin's lymphoma (cHL), a lymphoid malignancy of predominantly B cell origin, a number of these GFs and cytokines are produced by the mosaic of different cell types including the neoplastic giant multinuclear Reed-Sternberg and mononuclear Hodgkin's (HRS) cells. In addition, high levels of SDC1 expression have been detected in HRS cells [11]. Also, increased levels SDC1 in the sera of HL patients suggest shedding of its ectodomain [12]. This review highlights the relevant literature that provides insights into the role(s) of SDC-GF interactions in the pathogenesis and clinical course of cHL.

Expression of SDCs in different cellular subtypes

Expression of SDCs by normal B cells

In the hematopoietic system, SDC1 and SDC4 appear to be the most active syndecans in B cell lineage. SDC1 is expressed at

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distinct stages of differentiation of normal lymphoid cells (pre-B) and post-germinal center B cells, including mature plasma B cells and immunoblasts [13–19] (Fig. 1). In solid lymphatic tissue, SDC1 virtually controls the binding of B lymphocytes to the interstitial matrix. SDC4 is expressed in all stages of B cell development, except in the stem cell stage [20] (Fig. 1).

SDCs in Hodgkin's lymphoma

Although increasing evidence implicates SDCs in tumor development and progression, only SDC1 and SDC4 showed any association with HL. Elevated serum levels of SDC1 (sSDC1) has been reported for HL but without a prognostic significance, perhaps due to the small number of patients in the study [12]. Variable levels of SDC1 expression have been detected in subsets of primary HRS cells in some patients' biopsies [16, 21, 22]. A more recent immunohistochemical study showed that SDC1 is overexpressed by primary HRS cells of poor outcome and good outcome patients [11]. SDC1 is also transcriptionally upregulated by most of the cHL cell lines [11]. Stromal expression of SDC1 has been observed in 11/16 cHL cases [16]. SDC4 is expressed by most HL cell lines and by primary HRS cells [23, 24].

SDCs and plasma B Cell ancestry of HRS cells

SDC1 plays an important role in B cell differentiation and, by extension, the development of some B cell malignancies. As mentioned, SDC1 is expressed during the pre-B cell stages and by post-germinal center B cells. The HRS cells of HL typically lack B cell program due to epigenetic silencing. However, evidence suggests that these tumor cells are predominantly descendants of plasma B cells. Buettner et al. showed that several proteins that are important for the differentiation of B cells are also expressed by HRS cells of different subsets of HL patients, and in the samples examined, the tumor cells were SDC1-negative (SDC1−) [25]. Pax-5 [25], a transcription factor that limits the lymphoid progenitor cells to the B-lineage development by activating B-lineage-specific genes and suppressing non-B-lineage-specific genes, and IRF4 [25], which regulates germinal center B cell formation [26] and plasma cell differentiation [27], were consistently expressed by HRS cells [25]. Buettner and colleagues also showed that Bcl-6 [25], a transcription factor expressed by germinal center B cells, was detected in HRS cells of approximately 25 % of cHL cases [25]. Moreover, B lymphocyte-induced maturation protein-1 (Blimp-1), a key regulator of plasma cell differentiation, was expressed by a small proportion of HRS cells in 23 % of cHL cases [25]. The authors concluded that plasma cell differentiation might be initiated in a small subset of HRS cells but remains abortive.

A study was conducted to determine epigenetic similarities between cells of cHL and plasma cell myeloma since both share loss of gene expression program of mature B cells [28]. However, only a limited number of genes (e.g., IRF4/MUM1 and RYBP) were found to be jointly hyperacetylated and expressed in cHL and plasma cell myeloma cell lines [28]. Both the study by Buetner et al. [25] and Seitz et al. [28] suggest that the tumor cells of cHL are characterized by an abortive plasma cell phenotype with downregulation of B cell lineage-specific proteins.

Although the plasma cell phenotype is eradicated in HRS cells for most part, a subset of these cells do express SDC1 as well as other post-germinal center markers. In an immunohistochemical analysis of 101 cases of cHL, Bai et al. recognized three bcl6/CD10/MUM1/SDC1 immunophenotypes [29]. The late germinal center (GC)/early post-GC B cell-like immunophenotype were bcl6−/CD10−/MUM1+/SDC1− and occurred in 59/101 cases (59 %) [29]. Post-GC B cell-like immunophenotype showed a bcl6−/CD10−/MUM1+/SDC1+

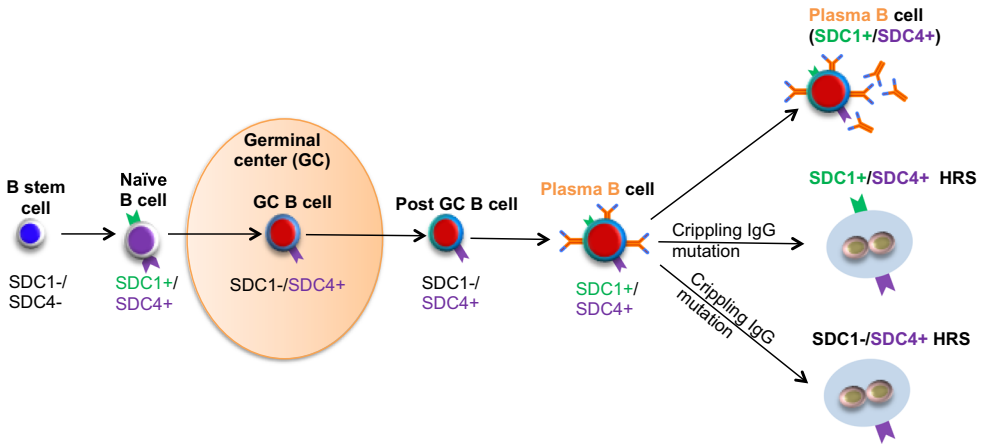

Fig. 1 Schematics showing the formation of SDC1+ HRS cells. In this interpretation, upon leaving the GC, post-GC B cells differentiate into plasma B cells which express SDC1 and BCR. The lineage that gives rise to HRS cells suffered crippling mutation of their IgG, lost most of their B cell programming (not represented), and escaped immune detection, but some of them retain the SDC1 signature. Except in the B stem cells, SDC4 is expressed by all stages of B cell differentiation and also by the HRS cells

immunophenotype in 24/101 cases (24 %) [29]. Indeterminate immunophenotype, which consisted of bcl6+/CD10−/MUM1+/SDC1+ in 14 cases and bcl6+/CD10−/MUM1+/SDC1+ in four cases, occurred in 18/101 cases (18 %) [29].

Studies in mice revealed that SDC1 expression by plasma B cells correlates with the onset of immunoglobulin release by B cells [30]. In HL, HRS cells do not produce functional immunoglobulin (IgG), a consequence of crippling mutations in immunoglobulin genes and a phenotype detected mostly in EBV-positive tumor cells [31]. Therefore, it is likely that some HRS cells continue to express SDC1 although they do not express IgG, unlike the myeloma neoplastic plasma cells that express both SDC1 and functional IgG.

In contrast to SDC1, SDC4 is expressed in all stages of B-lineage [20] and continues to be expressed by HRS cells [24]. Figure 1 summarizes the putative relationship between plasma B cell and SDC1/SDC4 HRS cells.

Shedding of SDC in Hodgkins' lymphoma

Shedding of SDC ectodomain in HL

The detection of soluble SDC1 in the sera of cancer patients suggests shedding of its ectodomain. Soluble SDC1 was detected in the sera of HL patients [12]. Shedding of SDC1 ectodomain is largely a consequence of the proteolytic activities of heparanase [32] and sheddases including metalloproteinases (MMPs), membrane-bound metalloproteinases (MT-MMP1) [33], and a disintegrin and metalloproteases (ADAM10, ADAM17) [34–36]. Shedding of SDC1 may further be accelerated by Rab-5 [37] and GFs [38]. Deregulated expression of these molecules by different cell types in the TM has been reported for HL [39–41]. In multiple myeloma (MM), the shedding is partly a consequence of heparanase-mediated activation of ERK signaling, which leads to the increased expression of matrix metalloproteinase-9 (MMP-9) [42]. In HL, ERK signaling is aberrantly active and it is shared with multiple signaling pathways (CD30, CD40, and RANK) that regulate cell proliferation and survival [43], but its role in SDC1 shedding remains unclear, in this neoplasm. The proteoglycan (PG) and glycosamineglycans (GAGS) of SDC1 are known to bind GFs and shuttle these cargoes to the nucleus [44, 45] although this has not been demonstrated in HL. However, given a molecular milieu that includes sheddases, SDC1, and GFs in the TM of HL, it is likely that these molecules constitute paracrine and autocrine networks that contribute to proteolytic cleavage of SDC1.

Shedding of SDC1 may be accelerated by inflammatory cytokines

Several inflammatory mediators, including inflammatory cytokines, enhance SDC1 shedding in vitro [38, 46–49], thereby mediating the potent pathophysiologic role(s) of SDC1 in cancer. HL is notorious for number of inflammatory cytokines (IL-1, 2, 5, 6, 7, 8, 13, 17, TGF-β, RANTES, TNF-a, CCL28, TARC), which are produced by either the HRS cells or by reactive cells in the TM. An in vitro study showed that RANTES (CCL5) accelerated shedding of SDC1 ectodomain in CCR5 (receptor for RANTES)-expressing Hela cells, an interaction that involves activation of MAP kinase signaling [49]. The same study showed that RANTES forms GAG-dependent complexes with the sSDC1 as well as with those of CD44. Intriguingly, SDC1 expression is also regulated by inflammatory cytokines [50]. Additionally, lymphoma (including HL) patients with progressive disease showed elevated levels of serum CD44 before and after treatment [51] and the expression of CD44 splice variant v10 by HRS cells in HL is associated with aggressive behavior and high risk of relapse (within 2–3 years) [52]. In HL, inflammatory cytokines may accelerate shedding of SDC1 and potentiate its putative tumorigenic roles in this malignancy (Fig. 2a).

Inhibition of SDC1 shedding by sphingosine-1-phosphate (S1P)

Sphingosine-1-phosphate (S1P) is a plasma-borne lipid, generated from the phosphorylation of sphingosine by isoenzymes sphingosine phosphate kinases 1 and 2 (Sphk1 and Sphk2). In the immune system, S1P is recognized as a major regulator of trafficking of T and B cells. S1P receptor, sphingosine-1-phosphate receptor (S1PR1), and Sphk1 are overexpressed by primary HRS cells and HL cell lines [11, 53, 54], which also express SDC1 [11]. S1P inhibits shedding of SDC1 from the surface of endothelial cells [55], a process that may reduce cell migration and metastasis in cancers where loss of SDC1 ectodomain is associated with increase metastatic potential [56], at least in an in vivo setting. In prostate cancer where SDC1 is overexpressed [57, 58], lower levels of circulating S1P, a consequence of downregulation of erythrocyte SphK1, strongly correlate with lymph node metastasis [59]. However, in vitro experiments showed that S1P potently stimulate migration HL cell lines SUPHD1 and KM-H2 [53] although the study did not indicate the level of SDC1 expression by these cell lines. In DLBCL, a B lymphoma in which SDC1 overexpression by primary tumor cells is a poor prognostic factor [60], sphingosine (Sph) (not S1P) induced cell death and blocked cell growth presumably independent of S1P receptors in different cell lines [61].

SDCs interact with APRIL to promote growth and proliferation of HRS cells

Studies showed that APRIL (a proliferation-inducing ligand) signaling via TACI (cyclophylin ligand interactor) and BCMA (B

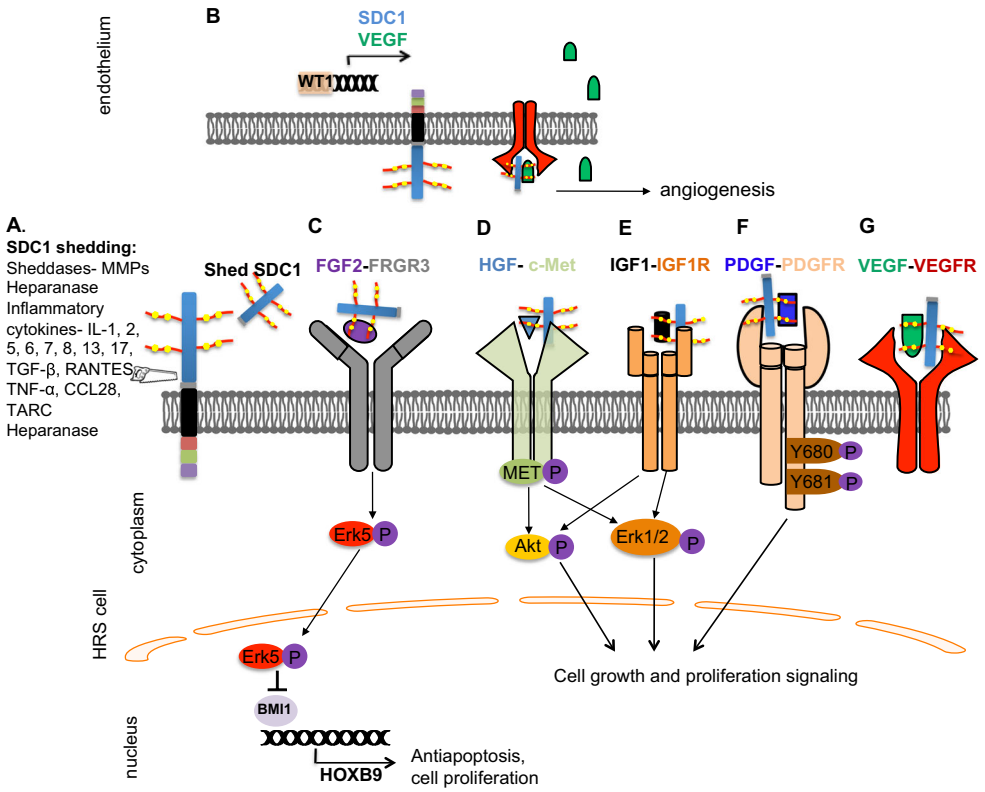

Fig. 2 Model of putative SDC1-mediated signaling of growth factor networks in HL. **a** The ectodomain of SDC1 can be shed by the activities of sheddases (such as MMPs), inflammatory cytokines, or heparanase. **b** WT1 upregulates endothelial expression of SDC1 and VEGF and promote angiogenesis. Also, sSDC1 (from either the epithelium or shed from HRS cells) may bind VEGF and stimulate angiogenesis. **c** Shed SDC1 mediate binding of FGF2 to FGFR3, resulting in phosphorylation of ERK5 which inhibit BMI1, resulting in HOXB9 upregulation. **d** Shed SDC1 mediated binding of HGF to c-MET, resulting in phosphorylation of MET (p-MET) and its downstream targets Akt (p-AKT) and Erk1/2 (p-ERK). **e** Shed SDC1 mediate the binding of IGF1 to its receptor IGF1R, also resulting in phosphorylation of Akt and Erk1/2. **f** Shed SDC1 mediated-of PDGF to PDGFR, resulting in phosphorylation at tyrosine residues 680 and 681 (Y680 and Y681, respectively). **g** Shed SDC1 also mediates the binding of VEGF to VEGFR. Activation of these signaling pathways lead to cell growth and proliferation, cell invasion, metastasis, angiogenesis, and cell survival. These pathways are also active in HL and may play a role in the behavior of HRS cells

cell maturation antigen) receptors is reinforced by HSPGs anchored on the cell membrane or associated with the extracellular matrix [62–64]. GAG side chains of cell-anchored and extracellular HSPGs bind a basic QKQKKQ amino acid sequence proximal to the amino terminus of APRIL, an interaction that promotes tumor growth of T cell origin [63, 64]. The resulting oligomerization of APRIL enhances TACI and BCMA signaling by promoting the formation of a highly efficient signaling network. HRS cells express APRIL and BAFF, TACI, and BCMA, but not BAFF-R. In the presence of BAFF or APRIL, TACI and BCMA provide cell-survival and growth-inducing signals to HRS cells. Chiu and colleagues showed that treatment of HRS cell lines that expressed SDC1 and SDC4, with heparinitase and heparinase, reduced binding of APRIL to the HRS cells [23]. The binding of APRIL to HRS cells was abrogated by heparin, a compound known to mimic extracellular HSPGs [23]. The authors also showed that APRIL-induced HRS cell proliferation can be increased in the presence of heparin but attenuated by heparinitase and heparinase [23]. This study highlights the importance of membrane-anchored and matrix-associated HSPGs on the proliferation of HRS cells via interaction with APRIL.

Angiogenesis

Evidence suggests that SDC1 may also mediate angiogenic signaling. In myeloma, shedding of SDC1 from the surface of the neoplastic plasma B cells is facilitated by heparanase, resulting in endothelial invasion and angiogenesis [8]. Studies also showed that levels of sSDC1 correlate positively with levels of hepatocyte growth factor (HGF) expression and regulate its signaling in myeloma [65, 66], a mechanism implicated in angiogensis. Also in myeloma, heparanase facilitates the upregulation of HGF and VEGF and SDC1 ectodomains bound to VEGF and presented VEGF to endothelial cells, initiating angiogenesis [8, 42, 67]. The pro-angiogenic role of SDC1 also appears to be dependent on its ectodomain that binds to αvβ3 and αvβ5 integrins. In vitro studies identify a short peptide that mimics the SDC1 ectodomain core protein (synstatin) that inhibit SDC1 interactions with both integrins, resulting in reduced endothelial cell invasion and slowing of tumor growth [8, 9].

Although evidence that support angiogenesis in HL is slowly emerging, elevated levels of pro-angiogenic molecules (namely

HGF, VEGF, TNF-alpha, and angiogenin) (including those that depend on SDC1 for enhanced binding and signaling) were detected in the sera of patients, before standard therapy, and subsequently decreased post treatment [68]. In the same study, HGF and VEGF correlated with IL-6 levels [68], another cytokine that can interact with SDC1 and also itself a negative prognostic factor in HL [69–71]. As mentioned, separate studies detected either sSDC1 or FGF2 in the sera of HL patients [12, 72]. In addition, the injection of HL cell lines KMH2, L428, and HDLM2 in conjunction with bone marrow mast cells into NOD/SCID mouse resulted in increase tumor vascularity [73]. However, the expression of a very few of the pro-angiogenic cytokines correlate with increase microvascular density (MVD). Immunohistochemical study showed strong expression of VEGF-D by HRS cells, and this correlated with a high number of tumor microvessels, suggesting a role for this GF in HL angiogenesis [74]. Vascular endothelial growth factor receptor-1 (VEGFR-1) and VEGFR-2, two important but highly related tyrosine kinase receptors, bind VEGF-A and promote survival of endothelial cells through the Raf-MEK-MAP kinase pathway [75, 76]. A retrospective study was conducted to evaluate the expression patterns of VEGF-A, VEGFR-1, and VEGFR-2 in cHL and NLPHL in a total of 194 cases [77]. The authors showed that HRS cells expressed VEGF-A, VEGFR-1, and VEGFR-2 in 90.3, 97.2, and 94.1 % of cases, respectively [77]. Importantly, there was a significant correlation between these markers and vessel branching [77]. Interestingly, morphometric data showed that increased angiogenesis, as evident by increased microvascularization, is a negative independent prognostic factor in HL [78]. Because sSDC1 can bind multiple pro-angiogenic cytokines, several of which are implicated in HL, and enhance their signaling, it is likely that the soluble form of this HSPG may have a pro-angiogenic role in HL (Fig. 2b).

SDC1-mediated angiogenesis in HL may further be potentiated by Wilm's tumor protein—WT1 (Fig. 2b). SDC1 is transcriptionally upregulated by WT1 [79], and it is expressed predominantly by epithelial cells [16] where it modulates neovasculization and cellular differentiation. In malignant lymph nodes of HL, WT1 is overexpressed by endothelial cells [80] where SDC1 is also likely to be expressed [81, 82]. As indicated, sSDC1 is known to bind to pro-angiogenic molecules such as FGF and VEGF (both of which are overexpressed in TM of HL) and activate them, thereby promoting endothelial cell invasion and angiogenesis. In addition, WT1 directly upregulates VEGF, resulting in increase angiogenesis [83, 84].

Exosome biogenesis

SDC1 is important in the biogenesis of exosomes, small 30–120-nm microvesicles released by cells into body fluids. The cargo of these microvessicles may consist of nucleic acids (RNAs, miRNAs) and proteins, which can be shuttled between tumor cells and host cells. Also, exosomes have been implicated in disease metastasis and relapse. HL cell lines have been shown to release exosomes containing CD30, which stimulates granulocytes to secrete IL-8, a pro-angiogenic cytokine [85]. Of interest, soluble CD30 (sCD30) is an independent poor prognostic marker in HL [86], and SDC1 binds to IL-8 and prolongs its biological functions [87]. Elevated levels of IL-8 in the sera of HL patients is associated with B symptoms [88]. Formation of exosomes is a consequence of the interaction of the SDC1 cytoplasmic domain with both syntenin and ALIX to form a complex that facilitates the budding of intraluminal vesicles within endosomal membranes [89]. In addition, SDC1 has been found in exosomes derived from cells of colorectal cancer [90], bladder cancer [91], and prostate cancer [92]. A search conducted for the expression of follicular dendritic cell markers by HRS cells turned up molecules associated with exosome physiologies. Syntenin was expressed by subsets of HRS cells [93]. And although no evidence of ALIX activities in HL has been reported to date, exosomes derived from aggressive B cell lymphoma were ALIX-positive [94]. These observations suggest that SDC1 may contribute to the synthesis of exosomes involved in the release of CD30 and perhaps contribute to the poor prognosis associated with sCD30. A possible mechanism may involve SDC1 mediating the synthesis and release of CD30+ exosomes, which then stimulate reactive cells to release IL-8, and proteolytically cleaved (either by heparanase or MMPs) SDC1 may bind to IL-8 thereby potentiating angiogenesis. The Epstein-Barr virus latent membrane protein 1 (LMP1), which has been localized to HRS cells [95, 96], may play a role in the exosomal release of FGF2 [97] into the biofluids of HL patients where significantly higher concentrations of it (FGF2) are associated with systemic symptoms and an erythrocyte sedimentation rate [72].

Putative SDC1-mediating signaling mechanisms

FGF2-FGFR3

FGF2-FGFR3 signaling has been demonstrated in hematological malignancies, including MM, lymphoma, and leukemia. Studies indicated that binding of FGFs to HSPG is required for signaling transmission through FGF high-affinity receptor [98, 99]. SDC1 forms ternary complexes with FGF2 ligand and its receptor (HSGAG:FGF:FGFR), a complex that stabilizes the receptor dimerization and promotes FGFR transphosphorylation. In MM, SDC1 [100], FGF2 [101], and FGFR3 [102] are overexpressed by the neoplastic plasma cells, signatures associated with a poor outcome [101–103]. This setting provides an autocrine mechanism for FGFR3 signaling. This mechanism may also be enhanced by a paracrine mode since SDC1 and FGF2 are elevated in serum of MM

patients [104]. The binding of FGF2 appears to be facilitated by heparanase. In melanoma cells, heparanase stimulates FGF2 signaling by degrading the cell surface heparan sulfate chains [105], a modification that enhances the binding of FGF2 to cell surfaces and leads to stimulation of ERK and focal adhesion kinase phosphorylation (FAK) [105]. Signaling pathways that involve the activation of ERK are also important regulators of cell growth and invasion and are altered during melanoma progression to metastatic phenotype [106, 107]. In MM, ERK is activated by insulin receptor signaling which is enhanced by heparanase [108]. And in HL, ERK signaling is activated by CD30, CD40, RANK [43], and FGF2 [109].

In HL, SDC1 [16, 21, 22, 110], FGF2 [111], and FGFR3 [111, 112] are overexpressed by HRS cells and other cell types in the TM, suggesting autocrine and paracrine mechanisms (Fig. 3). The oncogenic role(s) of FGFR3 is due to either its translocation or by activated mutation in different cancer types. In HL cell lines, multiple copies of FGFR3 have been reported [112], and it is constitutively active in primary HRS cells [111]. SDC1 [12] and FGF2 [72] are elevated in the sera of HL patients. These observations suggest an active role of SDC1-FGF2-FGRF3 signaling in HL pathogenesis. In HL, signaling arising from FGF2 occurred via ERK-5 pathway [109]. Treatment of the HL cell line KM-H2 with either an inhibitory antibody against the FGF2 protein or with genistein (an inhibitor of tyrosine kinase known to inhibit growth factor receptor signaling) resulted in significant decreases of nuclear phospho-ERK5 (p-*ERK5*) and *HOXB9* mRNA expression [109] (Table 1, Figs. 2 and 4). Overexpression of *HOXB9* promotes metastasis, tumor cell growth, and angiogenesis in cancers with a very poor clinical outcome [113, 114]. In addition, the expression and release of FGF2 by HL cell lines may be dependent on LMP1 expression [115].

VEGF-VEGFR

As indicated, SDC1-VEGF interaction appears important for angiogenesis and cellular invasion. In MM, this process is dependent on heparanse. Purushothaman et al. demonstrated that heparanase upregulated SDC1 shedding, via heparanase stimulation of ERK phosphorylation, with resulting upregulation of MMP-9, which then acted as a sheddase of SDC1 [42]. Interestingly, heparanase also mediates the upregulation of VEGF. VEGF likely binds to sSDC1 to stimulate endothelial cell invasion and angiogenesis. These roles may be mediated by the VEGFR signaling. Lamorte showed that SDC1 is involved in angiogenic phenotype of MM epithelial cells (MMECs) by promoting EC proliferation, survival, and modulating VEGF-VEGFR-2 signaling [116]. Rapraeger et al. showed that insulin-like growth factor 1 (IGF1R) coupling to SDC1 and αVβ3 integrin comprises a core activation mechanism activated by VE-cadherin that is necessary for VEGFR2 and integrin activation in the initial stages of endothelial cell dissemination during angiogenesis [117]. The TM of HL is populated with these molecular players. VEGF is expressed by HRS cells and by activated macrophages [118], and variants of VEGF proteins and their cognate receptors are upregulated in the sera of newly diagnosed cHL patients [119]. In addition, HRS cells expressed VEGF-A, VEGFR-1, and VEGFR-2 in 90.3, 97.2, and 94.1 % of cases, respectively, and this pattern correlated statistically with ramifications of blood vessels [77]. Since IGF1R is expressed by large subsets of HRS cells [120], it may be involved in enhancing the role of SDC1 in activation of VEGRF signaling [117], although details of αVβ3 integrin involvement is not known, in HL.

Several studies targeted the angiogenic roles of VEGF signaling in HL (Table 1). Evaluation of thalidomide, an inhibitor of VEGF [121] in combination with cyclophosphamide and

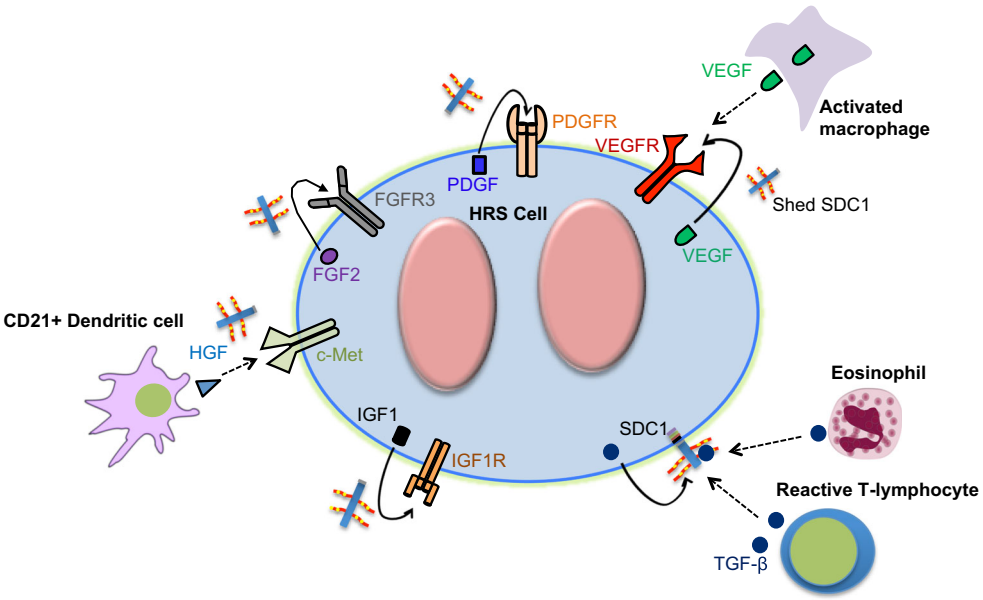

Fig. 3 Illustration of autocrine and paracrine (*dashed arrows*) interactions of growth factors (ligands for receptor tyrosine kinase—RTKs) and SDC1, the main HSPG, in the tumor microenvironment of HL. In this model, SDC1 mediate the binding of growth factors to their receptors on the surface of HRS cells, activating these pathways and thereby leading to cell growth, proliferation, and survival. Accumulation of sSDC1 may exaggerate the binding and produce more aggressive HRS cells

Table 1 Pre-clinical and clinical strategies for targeting growth factor signaling in Hodgkin's lymphoma

Pathway	Drug	Anti-tumor/clinical effects	Study
FGF2-FGFR	Genistein	Inhibit cell growth	[109]
VEGF-VEGFR	Bevacizumab (anti-VEGF monoclonal antibody)	Delay tumor growth in animal model; PR or CR in 3/5 cHP patients	[127]
	Lenalidomide	Objective and cytostatic responses	[124]
	Lenalidomide	2.7 % CR ($n = 1$), 16 % PR ($n = 6$), 13.8 % SD ($n = 5$)	[125]
	Lenalidomide (combined with cyclophosphamide)	38 % ORR (1 CR, 5 PR) 62 % clinical benefit ($n = 10$)	[126]
	Thalidomide (combined with vinblastine)	36 % RR (4 PR), 18 % SD ($n = 2$)	[123]
	Thalidomide (combined with cyclophosphamide and dexamethasone)	100 % CR ($n = 2$)	[122]
HGF-c-MET	SU11274 (a specific c-MET kinase inhibitor)	Cell cycle arrest	[136]
IGFR1	Cyclolignan picropodophyllin (a highly selective IGF1R inhibitor)	Cell cycle arrest and a decrease on cell viability	[120]
PDGF-PDGFR	Imatinib	Decrease cell survival and proliferation	[148]
	Sorafenib and lestaurtinib	Inhibit cell proliferation	[153]

dexamethasone [122] and vinblastine [123] in relapsed HL, showed clinical activities to this drug (thalidomide—Fig. 4). However, thalidomide was not further evaluated. Lenalidomide, a potent analog of thalidomide, has been investigated in HL (Fig. 4, Table 1). Treatment of a cohort of 38 heavily pretreated relapsed or refractory cHL patients with lenalidomide alone resulted in objective and cytostatic responses with modest toxicity [124]. In another study of lenalidomide as a single agent in heavily pretreated HL patients, Boll et al. reported 50 % overall response rate and low toxicity in the 12 subjects enrolled [125]. In addition, a recent study by Rueda et al. reported that lenalidomide combined with cyclophosphamide resulted in 38 % overall response rate (one complete remission and five partial responses), and clinical benefits to 62 %, in refractory and relapsing cHL patients who received autologous stem cell transplant [126]. Upon median follow-up of 19 months, 3-year progression-free and overall survival were 6 and 31 %, respectively [126].

The anti-tumor effects of bevacizumab, an anti-VEGF monoclonal antibody, were investigated in human HL xenografts in SCID mouse and in five patients with refractory/relapsed HL. In the animal model, bevacizumab treatment

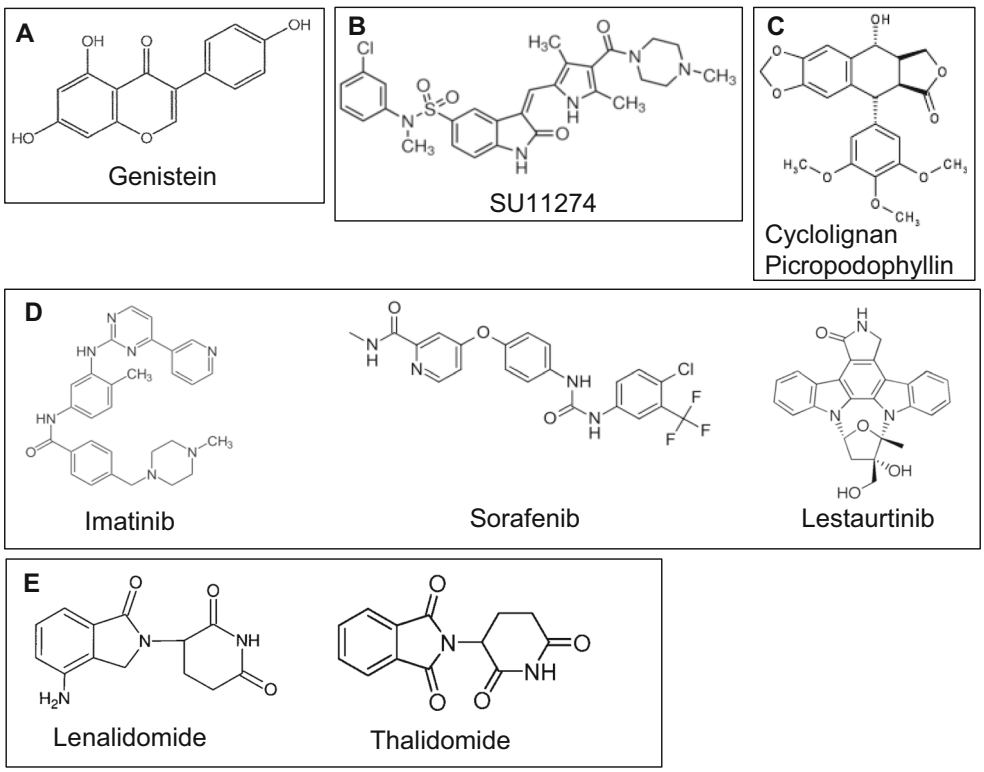

Fig. 4 Structures of receptor tyrosine kinase inhibitors used in Hodgkin's lymphoma. **a** Inhibitor of FGF2 signaling. **b** c-Met inhibitor used in blocking HGF-mediated signaling. **c** Inhibitor to IGF1-R signaling. **d** RTK inhibitors for PDGFR pathway. **e** Anti-VEGF and anti-angiogenesis molecules

resulted in significant delay in tumor growth, whereas three of the five human subjects treated with bevacizumab and gemcitabine showed complete response [127].

HGF-c-MET

In MM, overexpression of SDC1 is an independent negative prognostic factor [100] and elevated HGF levels predict a poor prognosis, short-term responses to therapies, and early relapses [66, 128, 129]. Also in MM, SDC1 promotes HGF-induced signaling through its receptor MET and downstream activation of Ras/MAPK and PI3/Akt signaling pathways, resulting in enhanced cell proliferation and survival [130]. In addition, high levels of nuclear heparanase resulted in upregulation of HGF and SDC1 shedding, enhancing the HGF signaling [67]. Nuclear heparanase also regulates the expression of SDC1 in MM [131]. These observations suggest a heparanase-SDC1-HGF regulatory loop in MM. In diffuse large B cell lymphoma (DLBCL), SDC1 overexpression by the tumor cells is associated with poor prognosis [60] and HGF induces MEK-dependent activation of ERK and PI3K-dependent phosphorylation of PKB, GSK3, and FOXO3a in MET+ tumor cells [132], suggesting a possible role of SDC1 in HGF signaling in B lymphomas. Also in DLBCL, HGF induces PI3K-dependent α4β1 integrin-mediated adhesion to VCAM-1 and fibronectin [132]. In HL, c-MET is expressed only by EBV+ cases [133]. However, only five out of six HL cell lines were c-MET+ although all six were HGF+ [134]. Teofili et al. reported the frequent expression of c-MET by HRS cells, surrounded by CD21+ follicular dendritic cells that express HGF [135] (Fig. 3), suggesting a paracrine mechanism. In addition, elevated serum levels of HGF were detected in HL patients and this was associated with B symptoms [135]. The c-MET+ HRS cells express α4β1 and α5β1 integrins [135], indicating the possible existence of HGF signaling pathway between HRS cells and the reactive cellular background. In vitro studies showed that although treatment of the c-MET+ HL cell line L428 with HGF resulted in increased phosphorylation of MET (p-MET), and upregulation of p-AKT and p-ERK1/2, there was no effect on cell proliferation [136], suggesting that SDC1-mediated binding of HGF to its receptor may be important for stimulating cell growth [65]. However, the c-MET inhibitor SU11274 (Fig. 4) suppressed cell growth by inducing G2/M cell cycle arrest [136]. Additionally, changes in plasma heparanase levels correlated with the response to treatment in HL pediatric patients [137]. Although P3-kinase/protein kinase B and RAS/mitogen-activated protein kinase networks are active in HL [138, 139], to date, there is no data to support their activation by HGF in this neoplasm, as occurred in MM [65]. However, the activities of heparanase, SDC1, HGF, and MET in the TM of HL suggest that these molecules constitute an active network that contribute to HL pathogenesis.

IGG1-IGF1R

In vitro studies showed that overexpression of SDC1 leads to the activation of IGF1R (and increased expression of Ets), resulting in increased proliferation of HT-1080 cells [140]. Beauvis et al. (2010) showed that SDC1 couples IGF1R to activate integrin signaling, promoting tumorigenic activities [141]. Although these mechanisms are independent of IGF1, they are enhanced by this ligand [141]. Interestingly, IGF1R coupling to SDC1 and αVβ3 integrin appears to be a core a mechanism activated by VE-cadherin that is necessary for VEGFR2 and integrin activation in the initial stages of endothelial cell dissemination during angiogenesis [117]. Of significance to lymphomas, Huang et al. showed that EBV infection increases αv, β3, and β5 integrin subunit mRNAs as well as upregulates the expression of the αv β3 integrin protein on human B lymphocytes [142] and about 40–50 % of cHL are EBV+. In HL, IGF1R is overexpressed by HRS cells in an almost all-or-none-fashion in 55 % of cHL patients, and this is associated with a favorable 5-year progression-free survival [120]. In this same study, the authors showed that addition of IGF1 to cell cultures resulted in increased phosphorylation of IGF1R and its downstream targets Akt (p-AKT) and Erk1/2 (p-ERK), producing an increase in cell proliferation [120] (Fig. 2e). In addition, inhibition of IGF1R with cyclolignan picropodophyllin (PPP, a highly selective IGF1R inhibitor) resulted in decreased cell growth and induced a G2/M cell cycle arrest, as indicated by decrease in pCcd2 and an increase in CyclinB1 levels [120]. Although there is no report on in vivo levels of IGF1 in HL, these observations suggest IGF1-IGFR1 may be an autocrine signaling which may be mediated or enhanced by SDC1. The cell lines used in this study express SDC1 [120, 143].

PDGF-PDGFR

PDGF (as well as other growth factors including IGF) appears to regulate the levels of HSPGs and variations in the expression of HSPGs correlate with the GF signaling activation by an auto-regulatory loop mechanism [143]. PDGF-BB treatment resulted in increased SDC1 mRNA expression [144]. Treatment of aggressive breast cancer cell lines exposed to PDGF-BB with imatinib reduces the cell surface expression of HSPGs (namely SDC2 and SDC4), thereby inhibiting cell proliferation, invasion, and migration [145], suggesting that HSPGs are involved in PDGF-mediated signaling. In HL, signaling by PDGF and its cognate receptor, platelet-derived growth factor receptor (PDGFR) may also be influenced by HSPGs (namely SDC1 and SDC4 as these are the only ones active in HL). Both PDGF [146, 147] and its receptor PDGFRA [148, 149], as well as EphrinB1 (another ligand for PDGFRA), are expressed by primary HRS cells in a proportion of HL patients. Intriguingly, cytoplasmic and nuclear

PDGF expression by primary HRS cells increase with disease progression in some cases [146] and shed SDC1 is known to bind and translocate GFs to the nucleus [44]. Also of interest, ephrins (namely EphrinB2) are known to upregulate the levels of SDC1 [150].

Activation of PDGFRA resulted in phosphorylation of specific intracellular tyrosines (mainly 680 and 681) of TRKA and of TRKB in HRS cells [148] (Fig. 2f). Of clinical relevance, high levels of PDGF have been detected in the sera of HL patients, but decreased after treatment [151]. Another study revealed that serum levels of PDGF in cHL patients remained elevated after treatment with ABVD and mediastinal radiation in stage IIA patients [152], indicating a possible role in resistance to radiation and chemotherapy. The expression of PDGF and PDGFR by the same HRS cells suggest an autocrine stimulation of tumor cell growth (Fig. 3). Inhibition of PDGFRA signaling with imatinib affected cell survival and proliferation of HL cell lines [148]. Sorafenib and lestaurtinib (Fig. 4), both already being used in clinical trials, inhibited proliferation of HRS cell lines, via deactivation of PDGF signaling, at concentrations achievable in patients [153]. In MM, PDGF-AB stimulates tumor growth and angiogenesis as evident by increased microvascular density (MVD) [154], which is also a negative independent prognostic factor in HL [78]. Given the affinity of HSPGs to bind to growth factors such as PDGFA [155], it is likely that SDC1 plays a role in tumorigenic signaling of PDGF-PDGFR in HL.

SDC4, expressed by HRS cells, may transduce signaling via PDGF-PDGFR pathway, which may also be related to changes in reactive oxygen species (ROS). SDC4 regulates generation of ROS through interactions with Nox1 [156]. Nox1 and its related homologs are NADPH oxidase family of enzymes responsible for the catalytic one-electron transfers of oxygen to generate superoxide or hydrogen peroxide. SDC4-mediated increases in ROS potentiate PDGF-mediated MAP kinase activation [156]. In addition, a syndecan(4)/PDGFR chimera resulted in increase MAPK activities [157]. In HL, although SDC4 [23, 24], PDGF [146, 147], PDGFR [148, 149], and MAP kinase activities [43] have been detected in the HRS cells, a SDC4-mediated increase in ROS may not potentiate PDGF-mediated MAP kinase activation, because CYBB (NOX2/gp91^{phox}), a homolog of Nox1, is downregulated, a consequence of gene deletion in some cases, thereby contributing to impairment of ROS synthesis by HRS cells [158]. However, an SDC4-PDGF interaction my produce other consequences in HL.

Signaling via TGF-β binding

SDCs also bind TGF-β to cell surface, [159, 160] including the surface of tumor cells. A study by Yang et al. showed that TGF-β binds to SDCs expressed on the plasma membrane of cell lines and primary tumor cells of the B cell origin, a process that may be involved in the regulation of intratumoral T cell differentiation in B cell non-Hodgkin's lymphoma [161]. It has been speculated that HS-mediated TGF-β binding is to protect TGF-β against proteolytic degradation [162]. The SDC-bound TGF-β in these instances still retains its active form, indicating a potent SDC-TGF-β interaction in tumorigenesis. In HL, various isoforms of TGF-β mRNA and proteins were detected by different types of cells including primary HRS cells [163], reactive T lymphocytes [164], and eosinophils [165], in the TM (Fig. 3). From a clinical standpoint, the presence of cytotoxic (TIA-1+ and granzyme B+) and regulatory T cells (FOXP3+) correlates with poor overall survival in HL [166–169]. In B cell non-Hodgkin's lymphoma (NHL), soluble TGF-β promote regulatory T (Treg) cells by enhancing expression of Foxp3 in CD4+ T cells and suppressed effector helper T (TH) cells by inhibiting expression of IFN-c and IL-17 [161]. In HL, TGF-β (and IL-10) produced by Treg and HRS cells (Fig. 3) exerts inhibitory effects on T cell effector functions, especially on cytotoxic T lymphocytes (CTLs) [170–173]. A study conducted on mostly stage IIA HL patients showed no decrease in the serum concentration of TGF-β after ABVD and mediastinal radiation, suggesting a possible role of TGF-β in resistance to both radiotherapy and chemotherapy in HL. The studies of TGF-β in HL paint an unfavorable role of this GF in the pathology of this lymphoma. However, given high expression of SDC1 in HL [11] and its binding of TGF-β to the surface of lymphoma cells [161], it is possible that SDC1 mediate the pathological role(s) of TGF-β in this malignancy. One possible role is the suppression of T cell functions. Additionally, separate studies showed that SDC1 and TGF-β may mediate expression levels of each other. RNA interference studies showed that changes in SDC1 resulted in altered levels of TGF-β [174]. In contrast, SDC1 expression is induced by TGF-β through the PKA-dependent pathway [175].

An SDC1-TGF-β signaling may also play a role in the generation of fibrosis in HL. TGF-β is known to induce fibrosis [176, 177] and it stimulates collagen synthesis [178], characteristics of some proportions of nodular sclerosing cHL subtype where there is strong expression of TGF-β [173]. Intriguingly, SDC1 is also a marker for fibrosis [179], and sSDC1 increases fibroblast proliferation and the release of TGF-β [180].

SDC1 and IL6

IL-6 is a pro-inflammatory cytokine produced by HRS cells and its overexpression is associated with poor prognosis and anemia [69, 70]. Studies indicated that IL-6 might have differential roles on the expression of SDC1. In B lymphoid cells, IL-6 regulates the expression of SDC1 at the post-transcriptional level. Exogenous application of IL-6 in growth medium of cultured murine B lymphoid cells resulted in decreased SDC1 expression, in a dose- and time-dependent manner, an effect that is reversible after IL-6 withdrawal [181]. In contrast, the overexpression of SDC1 resulted in a

ten-fold increase of IL-6 expression in malignant mesothelioma cells [182]. In breast cancer, SDC1 modulates the functions of β-integrin-dependent and IL-6-dependent functions in cell adhesion, migration, and resistance to irradiation [183]. In MM, the neoplastic plasma cells are SDC1+ and they also produce IL-6. In fact, large proportions of SDC1+/IL-6+ malignant cells detected in MM patients were associated with resistant relapse or primary refractory disease [184] and high blood levels of sSDC1 and IL-6 (and HGF) predict shorter survival [185]. These observation suggest that SDC1 and IL6 may involved a feedback loop, although no single study has demonstrated such, to date. Interestingly, HRS cells in HL tumor biopsies express either SDC1 [11] or IL-6 [186], and either of these proteins are elevated in the sera of HL patients [12, 187]; however, IL-6 levels correlate with poor prognosis [187]. In addition, the expression of IL-6 and its receptor by HRS cells suggest an autocrine role in the proliferation of these cells [186]. It is quite possible that the pathophysiological contributions of IL-6 in HL may be potentiated by SDC1.

Conclusion

Ample evidence suggests that SDCs mediate cancer development and progression by enhancing the binding of growth factors and cytokines to their cognate receptors, activating signaling pathways that give rise to angiogensis, cell growth and proliferation, and cellular invasion and metastasis. In HL, heparanase, inflammatory cytokines, and sheddases may cause shedding of SDC1 ectodomain. The shed SDC1 will then bind to and mediate the signaling of GFs such as FGF2, HGF, IGF1, PDGF, and VEGF, via autocrine and paracrine mechanisms. Pre-clinical and clinical studies in HL showed that inhibition a number of these pathways lead to decrease cell growth and proliferation (Table 1, Fig. 4). Perhaps these drug-inhibitory effects can be enhanced with greater understanding of the contribution of HSPGs (namely syndecans) to HL pathology. It is hopeful that the evidence discussed here will encourage future active research in the molecular function(s) of SDCs in the pathology of HL.

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Compliance with ethical standards

Conflicts of interest None

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