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The role of P-selectin in cancer-associated thrombosis and beyond

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ABSTRACT

Cells in our body interact with their environment by a large group of diverse cell adhesion molecules (CAMs). CAMs are involved in intercellular, intracellular, and cell-extra-cellular matrix (ECM) interactions. Besides their role in cell adhesion, CAMs regulate cell growth and motility, and various signal transduction pathways as well as inflammation. P-Selectin (SELP) is an adhesion molecule that belongs to the Selectin family of proteins, which are expressed by different cell types such as platelets, endothelial and immune cells, as well as several types of cancer cells. The high expression of SELP by activated platelets makes it an important component in the pathogenesis of thrombosis, in general, and in cancer-associated thrombosis (CAT), in particular. Interestingly, the mechanisms by which SELP mediates CAT are associated with tumor-promoting processes such as inflammation and metastasis establishment. Moreover, SELP was shown to have a role in tumor-host interactions and cancer immunity. Thus, SELP has been the focus of several studies exploring its role in cancer progression. In this review, we explore the current knowledge on the role of SELP in CAT, tumor biology and immunology, in addition to recent advances in SELP-targeted therapies.

1. Introduction

Selectins are vascular adhesion molecules expressed on the surface of platelets, endothelial cells, and leukocytes, mediating the initial step of immune cell infiltration from the bloodstream into the surrounding tissue. They are composed of an N-terminal C-type lectin domain, single EGF domain, a variable number of short consensus repeat (SCR) domains, a transmembrane region and a short cytoplasmic domain [1]. Selectins are further divided into E-, L- and P-Selectin. L-Selectin is mainly express by leucocytes, E-Selectin on endothelial cells and P-Selectin is mainly expressed by platelets. However, P-Selectin (SELP) is also expressed by inflamed endothelial cells and its translocation to the cell-membrane is regulated within minutes, while E-selectin requires de novo transcription and therefore, it is expressed on the cell surface a few hours following stimulation [2–4]. SELP is known to be involved in several immunological processes such as platelet activation and leukocyte recruitment and function [5–12]. P-Selectin glycoprotein ligand-1 (PSGL-1), the primary ligand for SELP, is a homodimer composed of disulphide-linked subunits creating a mucin-like transmembrane glycoprotein [13]. The N-terminus of the extracellular domain of PSGL-1 binds to all selectins although with the highest affinity to SELP. PSGL-1 is expressed by leukocytes, mediating their migration. Upon selectins binding, Src and Erk kinases are activated, regulating cellular function and cytokines production [14]. SELP is usually expressed as a dimer on the surface of endothelial cells and platelets. The dimeric form of SELP crosslinks PSGL-1 resulting in enhanced cell-adhesion [15]. Other than PSGL-1, CD44 and CD24 may also serve as functional SELP ligands [16,17]. Both are known to be involved in the epithelial-mesenchymal transition (EMT) process and expressed by cancer-stem cells [18]. CD24 was shown to regulate cancer cell migration, invasion and proliferation, and is used as a cancer-stem cell marker [19]. CD44 can be found in variant isoforms (CD44v) which can bind SELP. Various CD44v isoforms have been associated with different types of cancer. For instance, CD44v6 plays a role in pancreatic cancer metastasis and CD44v8-10 has been found to facilitate breast cancer lung metastasis [20]. Interestingly, SELP can be also secreted from the cells as a soluble protein (sSELP) which is most often found as a monomer [21]. The sSELP monomer contains the lectin and EGF domains which can bind and activate PSGL-1 [22]. Elevated plasma levels of circulating sSELP were detected in patients with cardiovascular disorders and several types of cancer [23]. As SELP is expressed by different cell types and it is involved in various biological processes in health and disease, its

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expression and function patterns affect tumor development and treatment. Here, we will review the current knowledge on the role of SELP in cancer-associated thrombosis (CAT) and tumor progression and will discuss the implications of targeting SELP for cancer therapy (Fig. 1).

2. SELP role in CAT

Cancer patients have higher risk of developing both venous and arterial thromboembolism (VTE and ATE, respectively). Although ATE is a less frequent and thus less studied complication of cancer [24], high incidence of ATE events such as ischemic heart disease and stroke were observed in cancer patients, mainly at 6 months post diagnosis, leading to a 3-fold increase in mortality [25,26]. Cancer-associated VTE is a well-known complication in many types of malignancies and was shown to be associated with cancer progression and increased mortality [27]. In fact, cancer patients have four-times higher risk of developing VTE than non-cancer patients, and six-times greater risk following chemotherapy administration [28,29]. Several mechanisms have been associated with the high risk of developing thrombosis in cancer patients. For instance, cancer cells have been shown to secrete Tissue Factor (TF) and other pro-coagulant factors, and to induce local inflammation which facilitate thrombus formation. An additional mechanism involves different adhesion molecules, including SELP, which mediate the adhesion of cancer cells to endothelial cells and platelets promoting blood clotting [29]. In addition, binding of SELP-expressing platelets to PSGL-1-expressing leukocytes facilitates the clot formation. This process is attributed to the formation of SELP-mediated leukocytes-platelets aggregates, containing TF [30]. Interestingly, activated leukocytes not only secrete cytokines that induce coagulation, but also produce microparticles containing TF and expressing PSGL-1 on their surface. These microvesicles bind to SELP expressed on activated platelets, thus promoting fibrin production [31]. Similar microparticles have been shown to be secreted by the cancer cells themselves [32]. Indeed, cancer patients with imaging-confirmed VTE exhibit higher levels of SELP detected in their blood samples [33]. Moreover, high levels of sSELP have been associated with cancer-associated VTE. Hence, measuring sSELP plasma levels may predict the risk for VTE in cancer patients [34]. In nasopharyngeal carcinoma patients, increased levels of sSELP were associated with high monocytes count, leading to local inflammation which facilitates both ATE and VTE [35]. This may be explained by previous findings which demonstrated that monocytes produce TF following activation with SELP [36]. Therefore, SELP inhibitors may offer a therapeutic approach to tackle several coagulation mechanisms and yield an anti-thrombosis effect. This was demonstrated by the development of an anti-SELP aptamer, ARC5692. Treatment with ARC5692 significantly promoted thrombus resolution and reduced vein wall fibrosis. This approach showed preferable results compared to heparin in non-human primate DVT model [37]. Moreover, administration of recombinant PSGL-1 (rPSGL-Ig, YSPSL) in cats was shown to be effective in reducing thrombus formation without affecting leukocyte adhesion and function [38]. These findings indicate that SELP can serve both as a prognostic marker and as a therapeutic target for CAT patients.

3. SELP mediates tumor-platelets interactions and cancer metastasis

The interactions between platelets and cancer cells have been shown to promote cancer cell growth and metastasis formation. Platelets secrete different tumor-supporting factors such as EGF, VEGF, FGF and TGF-β. As mentioned, SELP expression on platelets mediates their attachment to cancer cells. This process is not only involved in the initiation of thrombosis in cancer patients, but is also crucial in the metastatic cascade [39]. SELP-mediated binding of platelets to circulating tumor cells (CTCs) creates a platelet coating which facilitates their

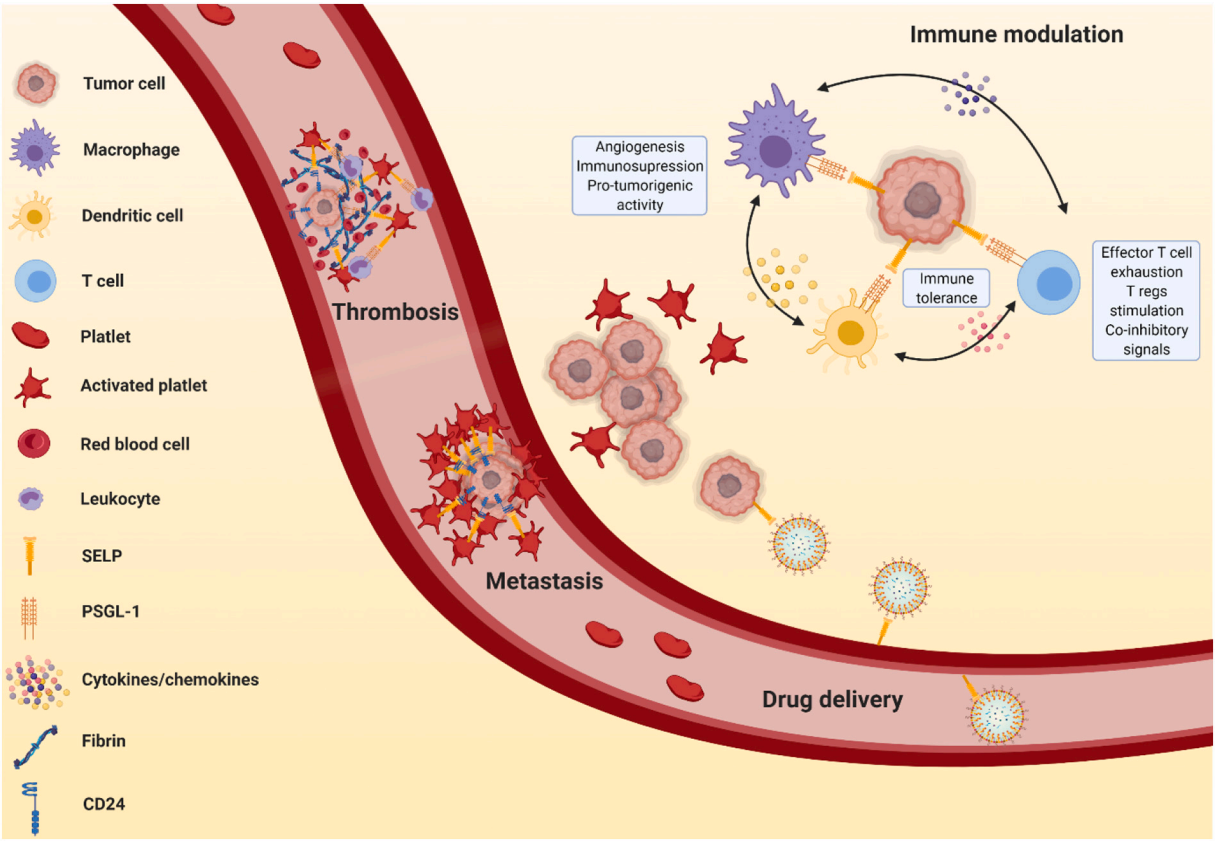

Fig. 1. Illustration showing the different roles of SELP in cancer progression. Created with Biorender.com.

Table 1
Anti-SELP treatments under clinical investigations. A table summarizing all the different therapeutic agents targeting SELP which have been, or are being evaluating in clinical trials for the treatment of sickle cell disease and cardiovascular or inflammatory conditions.

Product name	Crizanlizumab (SelG1, Adakveo)			PSI-697	Cylexin (CY-1503)	Bimosiamose (TBC1269)			Rivipansel (GMI-1070)	
Product description	Humanized monoclonal anti-P-selectin antibody.			Oral P-selectin inhibitor.	Synthetic analogue of sialyl Lewis X oligosaccharide.	Low-molecular weight nonoligosaccharide pan-selectin antagonist.			Novel small molecule glycomimetic pan-selectin antagonist.	
Purpose	Treatment of retinal vasculopathy with cerebral leukoencephalopathy (RVCL)	Study to assess safety and impact of SelG1 with or without Hydroxyurea therapy in Sickle Cell Disease patients with pain crises.	Crizanlizumab for treating COVID-19 vasculopathy (CRITICAL).	Study evaluating the effects of PSI-697 on platelets in subjects who smoke.	Cylexin for reduction of reperfusion injury in infant heart surgery.	Study to evaluate safety and efficacy of inhaled Bimosiamose for the treatment of patients with moderate to severe chronic obstructive pulmonary disease (COPD).	Study to evaluate the effect of bimosiamose on ozone induced sputum neutrophilia.	Safety and efficacy study of Bimosiamose cream to treat psoriasis.	Study of Intravenous GMI-1070 in adults with Sickle Cell Disease.	Study of GMI-1070 for the treatment of Sickle Cell Pain Crisis.
Phase	II	II	II	I	II, III	II	II	II	I, II	II
Results	Recruiting. February 9, 2021.	The P-selectin inhibitor SelG1 significantly reduced sickle cell pain crisis (SCPC) and appeared to be safe and well tolerated. Was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2020 for the prevention of recurrent vaso-occlusive crises (VOCs), or pain crises, in patients with sickle cell disease aged 16 years and older. https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3121034 https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-crizanlizumab-tmca-sickle-cell-disease	Completed, no results posted. January 19, 2021	PSI-697 did not inhibit basal or stimulated platelet-monocyte aggregate formation in humans. https://drugs.ncats.io/drug/LH1XC916ME	Cylexin was not effective in reducing myocardial infarctions in infants undergoing cardiac surgery.	Inhalation of Bimosiamose showed favourable anti-inflammatory effects on ozone-induced airway inflammation in healthy volunteers. Inhalation of Bimosiamose for 28 days was safe and well tolerated in patients with COPD	Completed, no results posted. January 6, 2010	Completed, no results posted. August 21, 2009	Results showed that the treatment was well-tolerated and produced no significant side effects. https://sicklecellanemianews.com/rivipansel-gmi-1070/	All subjects reached the composite primary end point of resolution of VOC.
Developers	Washington University School of Medicine. Principal Investigator: Jonathan Miner, MD/PhD. Reprixys Pharmaceutical Corporation (Novartis).			Pfizer.	Boston Children's Hospital. Principal	Revotar Biopharmaceuticals AG.			GlycoMimetics Incorporated. Pfizer.	

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Table 1 (*continued*)

Product name	Crizanlizumab (SelG1, Adakveo)		PSI-697	Cylexin (CY-1503)	Bimosiamose (TBC1269)			Rivipansel (GMI-1070)	
References	NCT04611880 [1]	NCT01895361	NCT04435184	Investigator: Jane W Newburger. NCT03860506 [2]	NCT00226369 [3, 4]	NCT01108913 [5-7]	NCT00962481	NCT00823693	NCT00911495 [8, 9]
NCT01119833 [10]									

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extravasation from the bloodstream and protects CTCs from being recognised by circulating immune cells, thus maintain their survival [40]. Moreover, the interactions between tumor cells, platelets and endothelial cells via SELP axis lead to local inflammatory state which supports the metastatic niche [41]. A large body of evidence suggests that SELP is involved in the spreading and metastasis of melanoma and colon cancer via platelet activation [42]. Indeed, it was shown that SELP deficiency reduced colon cancer lung metastasis by inhibiting tumor cells-platelets clumps formation [43]. Similarly, endothelial- and platelets- driven SELP expression was found to mediate melanoma lung metastasis [44]. One proposed mechanism involved CD24-SELP axis which was shown to facilitate cancer cells homing to the lungs [45]. These findings highlight the association between thrombotic events in cancer patients and tumor metastasis. Interestingly, treatment with heparin or its derivatives was shown to inhibit cancer metastasis by interfering with tumor cell-platelets as well as tumor cell-endothelial cell interactions in mouse models of lung and melanoma cancers. However, these mechanisms are yet to be fully understood [46]. Further research exploring these interactions may reveal novel mechanisms involved in cancer spreading, and pave the way to the development of new therapeutic and prognostic tools.

4. SELP is a key player in cancer immunology

The immune system and in particular T cells have the ability to specifically recognize tumor cells via their T cell receptor (TCR) and subsequently attack them. Although tumor cells are self-originated, they may express tumor-associated antigens (TAAs), which are generated from overexpressed or mutated proteins, thus identifying the tumor cell as abnormal, intruder or infected cell [47]. However, T cells require signals from the surrounding stroma and other immune cells, and express co-inhibitory receptors exploited by cancer cells to suppress their activation. This co-inhibitory receptor binding results in effector function inhibition, T cell apoptosis and immune tolerance [48]. Thus, cancer immunotherapies have been emerging as a promising therapeutic approach for cancer treatment, and many efforts are dedicated to development of novel immunomodulators in order to induce an effective anti-tumor immune response. SELP expression by endothelial cells, mediates leucocytes homing and their extravasation into the inflamed tissue. Recent studies have shown that PSGL-1 serves as an immune-checkpoint expressed on T cells [49]. Ligation of PSGL-1 promoted T cell exhaustion, the expression of co-inhibitory molecules such as PD-1, and impaired TCR signalling. In fact, downregulation of PSGL-1 resulted in enhanced secretion of pro-inflammatory cytokines and improved T cell activation against melanoma in mice. PSGL-1 deficient, melanoma bearing mice exhibited delayed tumor growth and prolonged survival compared to WT mice [50]. Moreover, SELP was shown to mediate the secretion of pro-tumorigenic cytokines such as IL-10 and TGF-β and to facilitate the infiltration of regulatory T cells [23], which have the ability to suppress cytotoxic T cells, and induce tissue repair and angiogenesis [51]. Dendritic cells (DCs) are antigen-presenting cells which play a vital role in mediating T cell response against tumor cells. Interestingly, SELP binding to PSGL-1 expressed on DCs results in tolerogenic activity leading to the suppression of cytotoxic T cells and accumulation T regulatory cells [52]. Another important component of cancer immunity are macrophages. They have the ability to attack cancer cells and stimulate T cell activation. However, tumor-associated macrophages (TAMs) have been shown to facilitate tumor progression and immune suppression. Although the exact role and activation state of TAMs are still unclear, reverting their phenotype to a more pro-inflammatory state has been shown to be a promising therapeutic approach for cancer patients [53]. Accumulating evidence suggests that SELP has a key role in mediating TAMs polarization. Interestingly, both SELP and its ligand PSGL-1 can be expressed by macrophages [54]. SELP binding to macrophages-expressed PSGL-1 stimulates cytokines secretion including CCL-2, which is important for TAMs recruitment and

function [14]. Indeed, SELP was shown to mediate monocyte adhesion to cerebral endothelial cells and its downregulation resulted in decreased numbers of activated macrophages in a model of acute hepatic inflammation [55]. Macrophage-cancer cell interactions via PSGL-1-SELP axis were found to promote drug-resistance in multiple myeloma through the activation of Src and Erk pathways [56]. Moreover, we have recently demonstrated that targeting SELP-PSGL-1 axis alters microglia/macrophages immunophenotype toward an anti-tumorigenic activation. We have showed that blocking SELP inhibits glioblastoma growth and enhances the immune response against the tumor [57]. Several studies suggested that SELP expression is downstream to the NF-kB pathway [58–62]. This may reveal the intracellular mechanisms by which SELP mediates TAMs phenotype. In cancer, NF-kB activation was shown to consequently activate STAT3 signalling, while STAT3-induced proteins maintain NF-kB activation [63]. Although the exact mechanisms are yet to be discovered, it was shown that NF-kB and STAT-3 activation promotes the anti-inflammatory phenotype of TAMs [64].

As SELP has a broad role in cancer immunology, affecting various immune components and mediating their interactions, its inhibition may serve as a powerful tool for cancer immunotherapy.

5. SELP as a target for cancer drug-delivery platforms

As SELP is expressed by activated endothelial cells, it serves as an attractive target for cancer drug delivery. Moreover, our group and others have previously shown that SELP is expressed by different cancer cells, including our recent report on the overexpression of SELP in glioblastoma cells and neighbouring stromal cells [65]. In this study, we designed a polyglycerol-sulfate (dPGS) nanocarrier conjugated to paclitaxel. The nanocarrier binds SELP via its sulfate modifications, mimicking SELP endogenous ligands. We showed that our dPGS nanocarrier is able to cross the blood-brain barrier (BBB) and selectively accumulate in the tumor site, targeting both the cancer cells and the tumor endothelium. Additional approach to target SELP is the use of fucoidan, a sulfated polysaccharide known as an anticoagulant [66]. Fucoidan nanoparticles were used for the delivery of doxorubicin to breast cancer tissue, and showed enhanced cellular uptake by SELP expressing cell lines, and increased cytotoxic activity in vivo [67]. In another study, fucoidan-decorated silica-carbon nano-onion nanoparticles were used to target the tumor-vasculature, delivering P-glycoprotein (P-gp) efflux pumps inhibitor to increase drug uptake specifically in the tumor site [68]. The nanoparticles were loaded with both P-gp inhibitor and doxorubicin and showed preferred anti-tumor activity compared to the free drugs. As SELP was found to be expressed by several cancer types, including lung, breast and ovarian cancer, fucoidan-based nanoparticles were used for the delivery of chemotherapeutic and targeted therapies such as MEK inhibitors for the treatment of various SELP-expressing tumors. Furthermore, it was demonstrated that radiation therapy stimulates SELP expression in the tumor microenvironment, and induces SELP expression in non-expressing Lewis lung carcinoma tumor cells. Irradiated tumors, treated with paclitaxel-loaded fucoidan nanoparticles showed increased drug accumulation in the tumor and delayed tumor growth compared to non-irradiated tumors. In addition, the same nanoparticles encapsulating doxorubicin showed the ability to reduce melanoma and breast cancer metastasis in mice [69]. Interestingly, SELP-targeted nanomedicines were also exploited for thrombosis therapy. Streptokinase (SK) loaded liposomal nanoparticles decorated with SELP and integrin GPIIb-IIIa binding peptides, were shown to efficiently target the thrombi site. SK facilitates the conversion of plasminogen to plasmin which breaks down fibrin. Delivering SK specifically to the thrombi site was therapeutically effective and reduced the haemorrhagic adverse effects observed with free SK [70]. Others have demonstrated the delivery of plasminogen activator (rt-PA) using fucoidan-based nanoparticles. These nanoparticles showed improved efficacy of rt-PA in a mouse model of venous thrombosis [71]. Potentially, targeting SELP for drug delivery may improve both thrombosis and cancer therapy. Combining thrombolytic agents with anti-cancer drugs in SELP-targeted nanosystems can serve as a dual therapy approach for CAT and prevent tumor metastasis.

6. Conclusions and future prospective

As we discuss the different roles of SELP in cancer progression and disease course, the use of SELP-targeted therapies may lead to improved therapeutic outcome. However, since SELP mediates various immune functions in pathological and physiological conditions, its inhibition may affect the balance of immune maintenance. This may lead to autoimmunity disorders, as blocking SELP-PSGL-1 axis facilitates the pro-inflammatory activation of macrophages and cytotoxic T cells [50]. Furthermore, blocking SELP-mediated cell adhesion may impair immune-trafficking and leukocyte rolling and recruitment [72], as well as platelet function in homoeostasis. Nonetheless, various studies have identified SELP as a therapeutic target for several pathological conditions such as cardiovascular diseases and sickle-cell anemia [73–77]. Furthermore, several clinical trials have shown safety and efficacy of anti-SELP neutralizing antibodies and small-molecule inhibitors in phase II trials for the above-mentioned conditions (Table 1). This demonstrates the therapeutic potential and safety of anti-SELP treatments.

As mentioned, radiation therapy, which serves as a standard of care for many cancer patients, was shown to increase SELP expression on endothelial cells on the lumen of angiogenic vessels [69,78]. This may affect the phenotype of recruited TAMs and T cells as well as other immune cells. Indeed, radiotherapy was shown to induced anti-inflammatory activation of macrophages [79] which may be related to the increase in SELP expression. On the contrary, various studies have shown that hypofractionated radiation may improve the efficacy of current immunotherapies [80]. Thus, adjusting the dosing and finding the precise treatment regimen may generate a synergetic effect of anti-SELP treatment and the standard radiation therapy. The elevated expression of SELP following radiation therapy may also be accounted for the high prevalence of CAT events. Ionizing radiation was shown to induce endothelial dysfunction and the expression of pro-coagulants factors, resulting in increased risk of thrombotic events following therapy [81]. Since the mechanisms underline thrombotic events in cancer patients differ from those in non-cancer patients, CAT might require different management [27]. Cancer patients have higher risk of recurrent thrombosis and bleeding events following treatment with anticoagulants. In addition, some anti-coagulants have been shown to interact with anti-cancer drugs [82]. As multiple mechanisms associating SELP with CAT, and standard chemo-radiation and anti-cancer targeted therapy increase thrombotic events, anti-SELP therapies may be the proper approach to treat cancer patients. Evaluating the combinatorial effect of anti-SELP agents and different chemotherapeutics and other cancer targeted therapies, will provide clinicians with the proper approach for exploiting SELP for cancer therapy. Moreover, as SELP mediates the recruitment and activation of T cells, anti-SELP treatment may improve the susceptibility of the tumor to existing immunotherapies, hence sensitizing non-responsive tumors to become immune checkpoint therapy (ICT)-responsive. To conclude, various tumor types exploit SELP axis in order to grow, invade distance tissues, and escape the immune system, thus deeper understanding of these signalling pathways may reveal important mechanisms in cancer biology which mediate fundamental processes in tumor progression.

Declaration of competing interest

R.S.-F. is a Board Director at Teva Pharmaceutical Industries Ltd. EY has no competing interests to declare.

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