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Dual implication of endothelial adhesion molecules in tumor progression and cancer immunity

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ABSTRACT

Adhesion molecules are proteins expressed at the surface of various cell types. Their main contribution to immunity is to allow the infiltration of immune cells in an inflamed site. In cancer, adhesion molecules have been shown to promote tumor dissemination favoring the development of metastasis. While adhesion molecule inhibition approaches were unsuccessful for cancer control, their importance for the generation of an immune response alone or in combination with immunotherapies has gained interest over the past years. Currently, the balance of adhesion molecules for tumor promotion/inhibition is unclear. Here we review the role of selectins, intercellular adhesion molecules (ICAM) and vascular cell adhesion molecules (VCAM) from the perspective of the dual contribution of adhesion molecules in tumor progression and immunity.

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Adhesion molecules; ICAM; immunotherapy; metastasis; selectins; VCAM

Introduction

Vascular endothelium endorses various functions owing to its structural role in separating blood from tissues. Endothelial cells (ECs), which cover the inner side of vessels, are responsible for vascular homeostasis and tone. In addition to vascular homeostasis [1,2], ECs are important for the innate immunity through the expression of Toll-Like receptors which contribute to the recruitment of immune cells to a target organ. Additionally, the upregulation of adhesion molecules at the surface of ECs supports the inflammatory state through leukocyte trafficking [3].

Adhesion molecules are transmembrane glycoproteins that contribute to the recruitment of circulating leukocytes from the blood to tissue. Immune cell ligands bind to the adhesion molecules which is followed by a cascade of interactions ultimately causing the extravasation of circulating immune cells [4,5].

Given their critical regulatory function between systemic circulation and tissues, EC and their adhesion molecules play a central role in cancer. While the tumor promoting effect of adhesion molecules through dissemination of cancer cells was well described, the capacity of these molecules to reprogram the tumor microenvironment (TME) and generate an immune response directed against tumors has created interest over the recent years, particularly with the development of immunotherapies [6–8]. Interestingly, the balance between tumor promotion (metastasis spread) and tumor inhibition (immunity development) is currently not established. Here we propose to review the dual implication of various endothelial adhesion molecules for cancer promotion/inhibition.

Overview of adhesion molecules: selectins, ICAM and VCAM

Selectins

Selectins represent a first group of cell adhesion molecules composed of three different glycoproteins, expressed either at the surface of endothelial cells (E-Selectin), leukocytes (L-Selectin) or platelets (P-Selectin) [9–12]. All three mediate the rolling of blood cells at the endothelial surface thus initiating leukocyte attachment to platelets, endothelial cells, and other leukocytes at sites of tissue injury and/or inflammation [13–15]. All the three members of the selectin family are type I transmembrane protein exhibiting an N-terminal lectin-like domain, an epidermal growth factor (EGF) domain and a variable short consensus repeat (CRP) domain [13]. Ligands binding to these molecules are numerous and diverse. Most of them carry sialylated, sulfated and/or fucosylated sequences [16]. The expression of E-Selectin is

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triggered by various inflammatory cytokines such as IL-1, TNF-α or bacterial endotoxin as a consequence of endothelial activation [17,18]. E-Selectin contributes to the recruitment of various immune populations including neutrophils, monocytes and T lymphocytes [9,19–21]. E-Selectin recognizes sialofucosylated lactosaminyl tetrasaccharides, prototypically sialyl Lewis x (sLex) and its structural isomer sialyl Lewis a (sLea) and binds to it in a calcium dependent manner [22].

P-Selectin is stored in the α-granules of platelets and Weibel-Palade bodies of endothelial cells. Following stimulation, notably by thrombin, P-Selectin is rapidly translocated at the surface of platelets or endothelial cells [23,24]. Ligands of P-Selectin – sLeX and P – selectin glycoprotein ligand 1 (PSGL–1) – are expressed at the surface of numerous immune cells including neutrophils and monocytes, thus supporting their adhesion to platelets or endothelial cells [14,15,25].

L-Selectin is constitutively expressed on most of immune cells including neutrophils, monocytes and lymphocytes. Its function is decreased through a down-regulation in its gene transcription, thus precluding its expression at the surface of the cells [26,27]. It interacts with sialomucin ligands either on vascular or tumoral compartment [28]. In addition to the adhesion to endothelium, L-Selectin holds an important role in leukocytes homing by allowing migration to lymph nodes [29,30].

Intercellular adhesion molecules

Intercellular adhesion molecules (ICAM) are a second group of adhesion molecules expressed at the surface of endothelial cells. The family is composed of five structurally related members, ICAM-1 to ICAM-5 characterized by the presence of extracellular immunoglobulin domains [31–33]. Preferred ligands for ICAM are a subgroup of integrins called β2-integrins. This subgroup is composed of four different integrins: CD11a/CD18 or LFA-1; CD11b/CD18 or Mac-1 or CR3; CD11c/CD18, or p150.95 or CR4; and CD11d/CD18. Each exhibits various expression pattern and binding capacities. For example, while LFA-1 is expressed only on leukocytes and binds only specific molecules close to ICAM, Mac-1 is expressed on myeloid cells and can bind up to 40 different molecules [34–36]. ICAM-1 is expressed at low levels on many cell types including epithelial cells, endothelial cells and immune cells [37]. In addition to contribution in homeostasis and injury repair, ICAM-1 is implicated in different steps of leukocytes trans-endothelial migration from rolling to adhesion to the endothelium mainly through the binding of its most reported ligand, LFA-1 [38–41]. Moreover, ICAM-1 is also an important contributor of the immunological synapse between antigen presenting cells and effector T-cells. While its role is not clearly understood, the dynamic expression of the molecule has been reported to be implicated in the priming of T-cells [42,43].

Contrarily to ICAM-1, with an expression closely dependent of inflammatory cytokines such as IL-1 or TNF-α, ICAM-2 is constitutively expressed at the surface of endothelial cells [44–47]. In addition to the leukocyte trafficking regulation role, ICAM-2 has also been reported to play a role in angiogenesis and in the control of the endothelial cell junction and barrier function [48–51]. Identified ligands for ICAM-2 are LFA-1 and DC-SIGN [52,53].

ICAM-3 is constitutively expressed at the surface of resting T lymphocytes and possesses a co-stimulatory activity in T lymphocytes. In addition, ICAM-3 is also implicated in cell contacts through its ability to induce LFA-1–ICAM-1 adhesion [54–59].

The expression of ICAM-4 is specific for erythrocytes [60]. In addition to the interaction with leukocytes and myeloid cells through CD11a/CD18 and CD11b/18 respectively, ICAM-4 can bind to αv integrins (αvβ1, αvβ3, and αvβ5) on non-hemopoietic cells, α4β1 on hemopoietic cells, and αIIbβ3 on platelets [61–64]. It has been reported that ICAM-4 could mediate interactions between red blood cells and macrophages [65]. Thus, ICAM-4 plays a role in cell interaction implicated in blood cells regulation, thrombosis and hemostasis.

ICAM-5 is the largest ICAM molecule, exhibiting nine extracellular immunoglobulin domains and is confined to the central nervous system with a surface expression on specific neurons [66]. ICAM-5 is acting at the interface of nervous and immune system. These interactions could result in microglia morphology shaping, regulation of synapses or cytokine release in the central nervous system [67–72].

Vascular cell adhesion molecule I

Vascular cell adhesion molecule I (VCAM-1) is a glycoprotein containing an extracellular domain with six or seven immunoglobulin (Ig)-like domains, a transmembrane domain, and a cytoplasmic domain [73]. VCAM-1 is mainly expressed on endothelial cells following pro-inflammatory cytokines such as TNF-α or exposition to reactive oxygen species (ROS). However, in condition of high and sustained inflammation, its expression has been reported on additional cell types including tissue macrophages, dendritic cells, bone marrow fibroblasts, myoblasts, oocytes, Kupffer cells, Sertoli cells, and cancer cells [74–77]. By binding to its leukocyte ligand α4β1/VLA-4 integrin, VCAM-1 plays a key role in leucocyte recruitment through

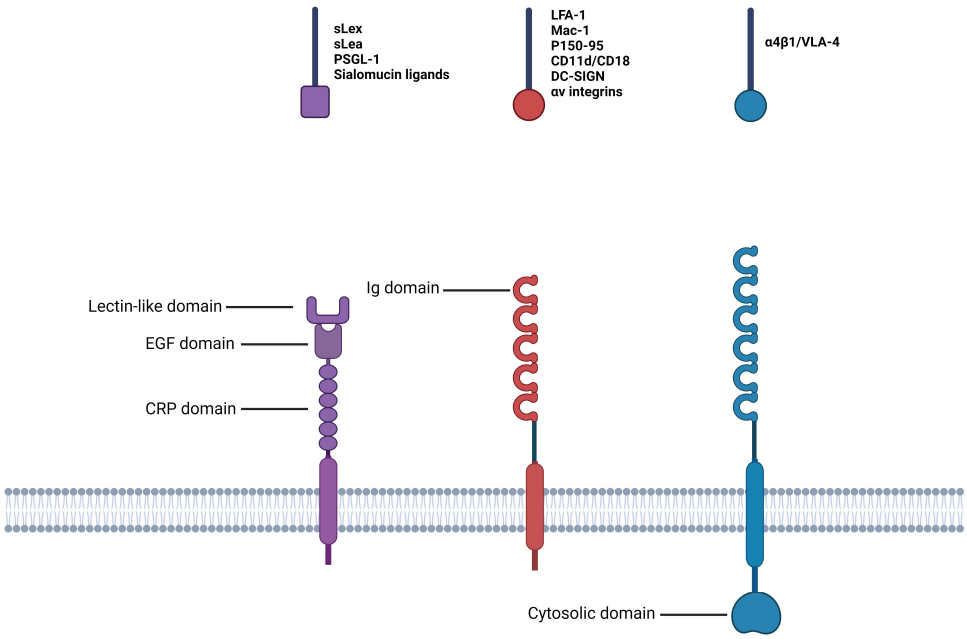
the adhesion of circulating immune cells to the endothelium and the activation of signaling pathways involved in trans-endothelial migration [78,79]. A summary of the structures of selectins, ICAMs and VCAMs is reported in Figure 1.

Contributions of endothelial adhesion molecules to tumor progression

Besides their pro-immune function, adhesion molecules have also been implicated in cancer progression through the promotion of metastasis.

Selectins

Tumors cells that disseminate from their primary location, do so by intravasating into the systemic circulation and extravasating into target metastasis organ sites. This process involves a cascade of distinct endothelial interaction steps. This is favored by the upregulated expression of selectin ligands (such as sLex, sLea, CD34 or MAdCAM-1) at the surface of cancer cells [80]. Thus, the extravasation of tumor cells at distant organs was shown to depend on the interaction of endothelial E-Selectin and tumor selectin ligands [81].



	SELECTINS	ICAM	VCAM
Pro-Tumoral	Dissemination and metastasis promotion	Metastasis promotion	Metastasis promotion
	Drug resistance	Drug resistance	Cancer angiogenesis
	Covering of CTCs	Cancer angiogenesis	Interaction between cancer cells and TAMs
	Cancer-associated thrombosis	Immune evasion	
Anti-Tumoral	Anti-tumor immunity infiltration	Anti-tumor immunity infiltration	Anti-tumor immunity infiltration
	Homing of T-Lymphocytes	Formation of tertiary lymphoid structures	Synergic effect with ICI
	Synergic effect with ICI	Effective target for CAR-T cells	

Figure 1. Structure of selectins, ICAM and VCAM adhesion molecules and their main respective ligands. Pro-tumoral and anti-tumoral roles are indicated. sLex: sialyl Lewis x, sLea: sialyl Lewis a, PSGL-1: P–selectin glycoprotein ligand 1, ig: immunoglobulin, EGF: epidermal growth factor; CRP: consensus repeat, CTCs: circulating tumor cells, ICI: immune checkpoints inhibitors, TAMs: tumor associated macrophages.

Consistently, high levels of selectin expression in cancer was shown to correlate with poor prognosis [82–84]. Recently, Tanio et al. [85] showed that the expression of E-Selectin ligands at the surface of clear cell renal cell carcinoma was a strong prognostic biomarker in patients. In hematologic cancers, E-Selectin expression at the surface of leukemic blasts was also associated with a worse prognosis [86,87]. Given the contribution of E-Selectin in metastasis, studies have tried to inhibit its expression to limit cancer dissemination. Brodt et al. [88] showed in a model of highly metastatic colon cancer that endothelial E-Selectin depletion significantly decreased the dissemination of colon cancer to the liver. Lange et al. [89] showed Bortezomib precluded the cytokine dependent expression of endothelial E-Selectin, thus impairing spontaneous lung metastasis *in vivo*. Interestingly, while ICAM-1 and VCAM-1 were depleted in presence of Bortezomib, authors concluded loss of E-Selectin alone was necessary to reduce adhesion of tumor cells. Khan et al. [90] observed a decrease in triple negative breast cancer metastasis in lungs following depletion of lung E, P and L-selectins. In an in vivo model of melanoma, Coppo et al. [91] confirmed that high levels of endothelial E-Selectin expression correlated with increased adhesion of tumor cells while inhibition with cimetidine was able to diminish tumor cell dissemination. In addition to its effect on metastasis, endothelial E-selectin is known to induce drug resistance [92]. In acute myeloid leukemia engrafted mice, E-selectin expressed by cancer cells was associated with a chemoresistance promoted through the Wnt pathway [93]. It has also been reported that PI3K/AKT/NF-κB pathway was an important mediator of chemoresistance induced by E-Selectin at the surface of tumor cells [94]. In solid cancer, Morita et al [95] showed that inhibition of vascular E-Selectin enhanced the anti-tumor effect of Doxorubicin and reduced tumor infiltration of protumoral macrophage M2.

P-Selectin expression has been reported to promote cancer dissemination. By binding P-Selectin, circulating tumor cells benefit from the cover of platelets protecting them from shear forces and immune cells [96]. This protumoral effect of P-Selectin and mucin/non-mucin-type glycoprotein have been well described in the past [97–101]. Kim et al. [97] investigated the contribution of P-Selectin in cancer progression and dissemination. They showed P-selectin-deficient mice harbored a slower growth of subcutaneous tumors and generated fewer lung metastases compared to control. Borsig et al. first described the contribution of P-Selectin to the dissemination of human carcinomas in immunodeficient mice [98] and later exposed its role in mediating the interactions between tumor cells and platelets in a murine adenocarcinoma in syngeneic immunocompetent mice [99]. Recent studies have also supported the contribution of P-Selectin to tumor progression: Cariello et al [102] showed in a colon cancer model that ablation of P-selectin in platelets significantly reduced tumor growth. Studying T cell lymphoma, Pereira et al. [103] found expression of the P-selectin ligand, PSGL-1, by the tumor cells was implicated in the development and dissemination of the cancer in different organs. The role of PSGL-1 was also investigated by Azab et al. [104] which drew the same conclusion in multiple myeloma. Zhang et al. [105] highlighted the preferred aggregation of low differentiated aggressive hepatocarcinoma cells with platelets through P-selectin. Conversely, abrogation of platelet aggregation with Clopidogrel attenuated platelet-tumor cell binding but also promoted hepatoma cell differentiation. Recently, the contribution of extracellular vesicles (EV) secreted by cancer cells in platelet aggregation through P-selectin expression have been investigated: Kim et al. [106] found that IL-8 released through cancer vesicles increased P-selectin expression at the surface of platelets and thus platelet aggregation. In addition, the level of platelet adhesion to vessel treated with cancer vesicles allowed to discriminate between breast cancer patients with and without metastasis. These results were supported by Gomes et al. [107] that showed aggressive breast cancer-derived EVs may contribute to cancer-associated thrombosis through an increase in platelet P-selectin exposure and platelet aggregation. This supports the implication of P-selectin in cancer-associated thrombosis previously described [108,109].

The contribution of L-Selectin to metastasis has been investigated in parallel to the contribution of E and/or P-selectin with similar implications [90,103,110]. Regarding the specific role of L-Selectin in cancer promotion, its expression in lymph node contributes to the dissemination of cancer cells in the lymphatic system [111]. Additionally, similarly to their interaction with platelets, tumor cells interact with circulating leucocytes by expressing L-Selectin ligands. These interactions favor survival of circulating tumor cells and the establishment of metastatic foci [112]. More specifically, research pointed out the critical role of myeloid cells in the dissemination of cancer cells through L-Selectin interaction. At the establishment of metastatic foci, an enhanced presence of CD11b-positive leukocytes associated with tumor cells was concomitantly detected, suggesting their involvement in this process [112]. Borsig et al. [99] observed a decrease in metastasis development in L-Selectin deficient mice. Interestingly, mice were deficient in T and B lymphocytes suggesting a specific contribution of neutrophils, monocytes, or NK cells. Läubli et al.

[113] showed interactions between leucocytes and cancer cells through L-Selectin increased the production of CCL5 by endothelial cells. Inhibition of CCL5-dependent monocyte recruitment during the early phase of metastasis strongly reduced tumor cell dissemination. Evidence implicating lymphocytes in cancer cells migration remains poor. Head and neck squamous cancer cells has been shown to be able to bind to lymphocyte in presence of a shear stress similar to lymphatic flow through L-Selectin [114].

ICAM

ICAM-1 contributes to cancer progression in different ways. As for other endothelial adhesion molecules, interactions with ICAM-1 on the surface of endothelium and its ligands expressed by the tumor cells favor tumor dissemination to secondary sites. This phenomenon has been highlighted as the suppression of ICAM-1 expression led to a decrease in cancer cell migration [115–117]. Chen et al also found that the expression of ICAM-1 by tumor cells was associated with a higher rate of bone metastasis and poorer prognosis in triple negative breast cancer [118]. This phenotype was partially explained by the ability of ICAM interactions to trigger the epithelial-to-mesenchymal transition program through TGF-β/SMAD. Taftaf et al investigated extensively the role of ICAM-1 at the surface of tumor cells in metastasis and found the molecule was involved in trans-endothelial migration but also in cluster formation of circulating tumor cells [119]. In a model of hepatocellular carcinoma, ICAM-1 was associated with increased vascular permeability through the VE-cadherin dependent interaction with endothelial cells [120]. In addition to its role in cancer dissemination, evidence suggest that ICAM-1 also plays a role in cancer angiogenesis. In triple negative breast cancer, Guo et al. [121] observed a reduction of vascular endothelial growth factor (VEGF) secretion in tumors of mice exposed to ICAM-1 inhibitors. Interestingly ICAM-1 expression levels in blood were reported as a reliable predictor of metastatic colorectal cancer response to bevacizumab (a VEGF receptor inhibitor) [122]. Similarly, in a clinical trial on non-small cell lung cancer (NSCLC), baseline plasma levels of ICAM-1 were found to be prognostic for survival and predictive of response to chemotherapy with or without bevacizumab: indeed, low baseline levels of ICAM-1 were associated with better survival and better response to bevacizumab [123]. More generally, ICAM-1 is reported as a prognostic cancer marker in oral cancer but also breast, colorectal and gastric cancer [124–127]. Pro-tumoral role of the other ICAM molecules are less investigated. ICAM-2 inhibition in the tumor promoted anti-tumor response in colon carcinomas mouse models [128]. A pro-tumoral role of ICAM-3 seems to be largely mediated through the PI3k/Akt pathway. Kim et al assessed the contribution of ICAM-3 in cancer cells for their proliferation through the PI3k/Akt pathway [129]. Using the same pathway and CREB pathway, ICAM-3 expression favors cancer invasiveness by upregulating expression of MMP-2 and MMP-9 [130]. In addition to cell proliferation and dissemination, activation of this pathway by ICAM-3 also promote anti-cancer drug resistance [131]. Finally, ICAM-3 expressed by tumor cells is also associated with a poor prognosis either favoring radiation resistance [132] or immune evasion [133]. ICAM-5 seems to play a role in tumorigenesis and perineural invasion through the PI3K/Akt pathway as well. Indeed, Maruya and colleagues [134] observed a high incidence of perineural invasion in ICAM-5 rich specimen and a decreased ICAM-5 expression following PI3K inhibition.

VCAM-1

VCAM-1 has been reported to be expressed by numerous tumor cell types of pancreatic, breast and gastric cancers [135–138]. This expression enables the interaction of cancer cells with cancer associated macrophages harboring α4-integrins leading to tumor growth support [136]. Similar phenomena were observed in glioblastoma where exposure to IL-1β induced the expression of VCAM-1 and ICAM-1 on tumor cells. Their presence allowed the adhesion and polarization of tumor-associated monocytes [139]. In pancreatic cancer, lactate production induced by VCAM-1 from pancreatic cancer cells with enhanced aerobic glycolysis activated macrophages to a TAM-like phenotype [135]. The contribution of VCAM-1 to metastasis is well described in literature [77]. CXCL1 and CXCL13 are able to induce VCAM-1 expression in osteosarcoma cells through the NF-kB pathway, which in turns favors VCAM-1 dependent migration of cells [140,141]. In a melanoma model, Klemke et al. [142] demonstrated that the migration of cancers cell lines was dependent on the VLA-4 and VCAM-1 interaction at the endothelial level. Authors also pointed out that the affinity between these two molecules was positively correlated to the aggressiveness of the cancer cell line. Investigating the specialized environment of the brain, Sikpa et al. [143] deciphered the implication of VCAM-1 in the formation of brain metastasis. Upregulation of VCAM-1 in the vessels following cerebrovascular inflammation promoted the interaction of circulating tumor cells with endothelial cells and thus their extravasation.

Inflammation also drove lymphatic permeability and invasion by cancer cells when VCAM-1 was induced in lymphatic endothelial cells [144]. Regarding vascular permeability, M2 macrophages seemed to contribute to vascular permeability via the VCAM1/RAC1/ROS/p-PYK2/p-VE-cadherin cascade initiated by interaction between VLA4 and VCAM-1 on endothelial cells in ovarian cancer [145]. Not only surface VCAM-1, but also secreted VCAM-1 seems to promote tumor progression. Indeed, cancer associated fibroblasts are able to secrete VCAM-1 which in turns increase growth and invasion through the AKT and MAPK pathways in lung cancer cells [146]. The expression of VCAM-1 is closely related to angiogenesis and VEGF secretion by tumor cells although their relative influence to each other remains complex. Sustained levels of VEGF correlated with low levels of VCAM-1 in the endothelium that may consist in a mechanism of defense from tumor cells promoting their immune evasion by precluding immune infiltration [147,148]. On the other hand, studies have reported areas of high microvessel density that correlated with high VCAM-1 expression in various cancers [137,149]. Sano et al [150] observed a reduction of tumor angiogenesis which led to a decreased tumor growth and metastasis in presence of endothelial VCAM-1 inhibition. In human samples, the use of VCAM-1 as prognostic marker has grown in interest. In the plasma of preoperative patients of urothelial bladder carcinoma, elevated level of VCAM-1 was associated with aggressive features such as lymph-node-metastasis or ≥pT3 disease while no correlation with overall survival (OS) or progression free survival (PFS) could be assessed [151]. In the tumor tissue of nasopharyngeal carcinomas, VCAM-1 was associated with chemotherapy resistance, shorter progression free (PFS) and overall survival (OS) [152]. Additionally, high levels of soluble VCAM-1 were also associated with shorter PFS and OS in advanced breast cancer patients [153]. Conversely, in metastatic colorectal cancer, soluble VCAM-1 appears to improve OS benefit in the context of a regorafenib treatment [154].

Impact of endothelial adhesion molecules on anti-tumor immunity in the context of immunotherapies

Adhesion molecules also harbor an anti-tumor role by re-shaping the tumor immune microenvironment. This role could be of increasing importance particularly in the context of immunotherapies.

Selectins

While selectins expressed at distant locations from the tumor can participate to the invasion of target tissues by circulating tumor cells, the expression of E-Selectin ligands by the immune cells may have a determinant role in preventing tumor progression [155]. Endothelial P and L-Selectin inhibition in a model of colon carcinoma and melanoma was associated to enhanced tumor growth, which may be related to the lack of monocyte infiltration within tumors [156]. The importance of selectins in cancer immunity have been further confirmed by Stark et al. [157]. In their study, the contribution of selectins in E/P/L-selectin deficient mice was highlighted: compared to control mice, the infiltration of CD8+ T cells into the draining lymph nodes and tumors was impaired thus resulting in significantly shorter survival. Weishaupt et al [158], suggested that the induction of endothelial E-Selectin and ICAM-1 was essential to improve tumor control in metastatic melanoma. For treatments involving CAR-T-cells, the expression of E-Selectin at the target site was shown to be mandatory for CAR T-cells to reach the target for effectiveness [159]. While the activation status of lymphocytes is critical for tumor control, the functional homing of effector lymphocytes promoted by selectins is also required. Indeed, Aires et al, showed that selectin ligand-deficient mice were not able to limit tumor growth when compared to controls [160]. Interestingly, these differences were unrelated to antigen recognition or effector T-cell function, pointing out an important role for selectins in getting the effector cells in the right location.

Among selectins, L-Selectin has been described as a major molecule for the development of an immunity directed against tumors. Indeed, L-Selectin facilitates lymphocyte homing to lymph nodes (LN). L-Selectin blockade prevented the homing of lymphocytes in lymph nodes and primary tumor sites, thus impairing the development of a specific cytotoxic T cell response [161]. Myeloid derived suppressor cells (MDSC) were able to target lymphocytes homing to lymph nodes by cleaving L-selectin expressed by T-cells with surface ADAM17 which resulted in a decreased antigen-specific response [162,163]. Consequently, the targeting of MDSC with doxorubicin improved the killing efficacy of cytotoxic lymphocytes. The elimination of tumors by lymphocytes was antigen-specific and resulted from an upregulation of CD3ζ and L-selectin in cytotoxic T-cells [164]. L-Selectin has also been investigated in the context of immunotherapy. Watson et al. [165] found that

mice deficient for L-Selectin showed faster tumor progression. Interestingly, mice with persistent L-Selectin expression at the surface of T cells had a reduced tumor growth. Tsui et al [166] focused on exhausted T-cells and restoration of function after PD1 blockade. They identified a subpopulation of exhausted T cells specifically expressing L-Selectin that exclusively proliferated in response to anti-PD-1 therapy. Finally, Kumari et al. [167] confirmed the implication of L-Selectin expressed by B-cells and T-cells with the positive outcomes in breast cancer samples from patients. They found a strong correlation between the SELL gene and a pro-inflammatory tumor microenvironment, including B- T-cells and M1 macrophages. High SELL expression was associated with favorable survival in breast cancer as well. These observations were later confirmed in colorectal cancer patient samples and in breast when SELL was upregulated in tumor tissues [168].

ICAM

The crucial role of ICAM-1 in limiting tumor progression was reported by several studies. The depletion of ICAM-1 in T-cells led to a lack of immune infiltration in tumors with poor cancer control [169–171]. It had been observed in breast cancer that patients with elevated ICAM-1 tumor levels had a better survival, Regev et al found that while ICAM-1 deletion did not affect primary breast tumor growth, there was an increase in spontaneous metastasis to the lungs in ICAM-1 KO models. The control of lung metastasis was mediated by neutrophils, binding ICAM-1 expressed in the lung vasculature [172]. Figenschau et al highlighted ICAM-1 expression by cancer cells was associated with tertiary lymphoid structure formation within tumors [173]. In malignant melanoma, the primary and metastatic tumor control were affected by the loss of L-Selectin and/or ICAM-1 on tumor cells [174]. This phenotype was associated with a general depletion in the infiltrating populations including natural killer (NK) cells, CD4+ and CD8+ T cells, but also pro-inflammatory cytokines such as IFN-γ or TNF-α. The absence of ICAM-1 may also contribute to the resistance of cancer cells by precluding specific immune cells to interact with the tumor tissue. Indeed, Liu et al. [175] reported pancreatic tumor cells to be resistant to γδ-T-cells because of the poor binding occurring in absence of ICAM-1 or ICAM-2 at the surface of the cancer cells. The transfection of resistant cells with ICAM-1 or ICAM-2 subsequently restored the sensitivity of pancreatic tumor cells to γδ-T-cells. Interactions between immune cells and cancer cells through ICAM-1 are also responsible for intratumoral retention of activated CD8+ T-cells. As demonstrated by Yanguas et al. [176] the blocking of ICAM-1 in the tumor reduced the clusters of lymphocytes inside the tumors by allowing their homing to LN. Yang et al. [177] observed that ICAM-1 expression in the tumor inversely correlated with macrophage infiltration while deficiency in ICAM-1 resulted in the specific increase in M2 macrophages population. Interestingly, the increase in M2 subpopulation results from a polarization of macrophages toward this phenotype that appeared to be enhanced by an increase of efferocytosis of apoptotic cells through the PI3K/AKT pathway.

The impact of ICAM-1 on the response to immunotherapy remains a matter of debate. The soluble fraction of ICAM-1 in the blood of hepatocellular carcinoma patients correlated positively with a better OS and a lower recurrence rate but was also predictive of a poor response to immune checkpoint inhibition [178]. However, Taggart et al observed an increase in immune populations following combined CTLA-4/PD-1 treatment. An upregulation of ICAM-1 and VCAM-1 in the tumor following treatment appeared to be responsible for this phenotype [179]. This relation was also reported by Schneider et al, who observed an increase in ICAM-1 binding following anti-CTLA-4 exposition [180]. In combination with bevacizumab, anti-CTLA-4 enhanced tumor infiltration by promoting E-Selectin, ICAM-1 and VCAM-1 at the surface of melanoma cells [181]. In relation with the CAR T-cells field, ICAM-1 at the surface of tumor cells was reported as a good target for CAR T-cells in reason of its wide expression across tumors [182]. Interestingly, PD1 blockade in combination with ICAM-directed CAR T-cell enhanced tumor cells eradication compared to CAR T-cell alone, suggesting a synergic effect [183]. In addition, the expression of ICAM-1 at the surface of Ewing's sarcoma following exposure to pro-inflammatory cytokines improved the recognition and killing of the tumor cells by specific CAR T-cell [184].

Of note, ICAM-2 is specifically reported as increasing anti-tumor immunity. Transduction of ICAM-2 by intratumoral injection significantly inhibited tumor growth in subcutaneous gastric tumors. The reduction of tumors growth was associated with an increase in NK cells infiltration [185]. ICAM-2 also promoted survival of immune cells. Through the activation of PI3K/AKT pathway, ICAM-2 precluded CD19+ cells from apoptosis [186].

VCAM-1

VCAM-1 endothelial expression, as the previous adhesion molecules, exerts its anti-tumoral contribution through the recruitment of immune cells directed against cancer. In tumors, endothelial cells are known to be anergic and not efficiently promote immune infiltration. In an attempt to restore immune response inside the tumors, Nakajima et al. [187] treated pancreatic tumors cell with Embelin to increase levels of VCAM-1 and E-Selectin in endothelial cells within tumors. In response to this upregulation, authors noted a higher infiltration of anti-tumor immune cells, which ultimately led to an improved tumor control. Conversely, following inhibition, Sasaki et al highlighted the crucial role of VLA-4/VCAM-1 interaction in immune infiltration of tumors. More specifically, Th1 T-cell infiltration was restricted when VCAM-1 at their surface was abrogated, leading to a loss of immune mediated tumor control [188,189]. Campisi et al showed that cGAS-STING signaling from tumor cells ultimately increased the expression of E-Selectin, ICAM-1 and VCAM-1 on tumor endothelium, thus enhancing immune cell extravasation [190].

VCAM-1 appears to enhance the response to immunotherapy. Riegler et al. [191] showed that endothelial VCAM-1 was an interesting in vivo predictor of both immune infiltration and response to immunotherapy in a preclinical model of MC38 tumors. Endothelial VCAM-1 density obtained by noninvasive imaging correlated with tumor infiltration and response to PDL-1 blockade. Moreover, blocking interaction between T-cell and VCAM precluded tumor rejection. Studies on patients also support the beneficial effect of VCAM-1 in checkpoint blockade. In NSCLC, high serum levels of VCAM-1 correlated with an improved OS in patients treated with second line nivolumab [192]. In the context of cancer vaccination, the combination of sunitinib and peptic-pulsed dendritic vaccines displayed the best results in tumor regression compared to control groups. It appears sunitinib contributed to increase the expression of VCAM-1 at the surface of vascular cells, allowing an improved recruitment of vaccination-induced cytotoxic T-cell [193]. Results are similar to Garbi et al. [194] who treated pancreatic islet cell carcinomas with antigen-specific vaccination (Tag) and vaccination to oligodeoxynucleotides (ODN) with cytosine-guanine-rich (CpG) motifs (CpG-ODN) to enhance immunity generated by Tag. Interestingly, while Tag successfully primed T-cell, immune cells were not able to penetrate into the tumor tissue. CpG-ODN concomitant exposition acted as a pro-inflammatory agent which upregulated ICAM-1 and VCAM-1 at the surface of vascular cells. This systemic stimulation ultimately enhanced the extravasation of primed T-cells, which translated into an improved tumor control. Both pro-tumoral and anti-tumoral impacts of adhesion molecules are recapitulated in Table 1. The contribution of endothelial adhesion molecules for their interaction with tumor and immune cells is resumed in Figure 2.

Overall, data from the literature suggests that adhesion molecules such as E-Selectin, ICAM-1 and VCAM-1 can either favor (through vascular tumor cell intravasation) or limit (through enhanced tumor immune infiltration and efficient immune response development) tumor growth, Table 2. Changes in the expression of ICAM-1 at the surface of newly formed vessels can affect T-cell infiltration. Several studies reported the emergence of poorly perfused and permeable vessels following expression of pro-angiogenic factors in tumors [195,196]. At the surface of those aberrant vessels, clustering defect of ICAM-1 and VCAM-1 induced by VEGF-A are partially responsible for the hampering of immune cell infiltration [197]. In addition, it has been reported that VEGF reduces the expression of ICAM-1, E-Selectin and VCAM-1 at the surface of endothelial cells [198,199]. Therefore, treatments aiming to relieve the vascular anergy in the aberrant tumor vasculature could enhance immune cells infiltration through adhesion molecule expression.

Summary: selectins, ICAM-1, VCAM-1: pro or anti-tumoral role?

In light of this review, adhesion molecules have a broad impact on tumors and their microenvironment. Therefore, their study and therapeutic activation/inhibition should be balanced with the perspective that they can promote (metastasis development) or inhibit (anti-tumor immune microenvironment remodeling) cancer progression. Their study should thus take into consideration the location of expression, the cancer type, its immune microenvironment and metastatic potential.

Specifically, E-Selectin tumor or distant site endothelial expression promotes cancer progression via chemoresistance [93,94] and cancer cell extravasation in distant organs respectively [89,90]. Conversely, E-Selectin expression in endothelial cells at the primary tumor site promotes better local control because of better immune cell infiltration [156,159]. The impact of L-Selectin was similar although cancer dissemination was mostly promoted via lymphatics [111,114,162,164]. Finally, tumor P-Selectin mostly had a tumor dissemination role by protecting, via platelet aggregation, cancer cells from blood stream shear stress [98,99].

Table 1. Contribution of adhesion molecules in tumor progression and antitumor response establishment.

Adhesion molecules	Pro-tumor role	Anti-tumor role	Models used
E-Selectin	Metastasis promotion by extravasation into tissue [88–90] Drug resistance through NF-kB and Wnt pathway [92–95]	Anti-tumor immunity infiltration [156,157,160]	Pro-tumor role: Murine cancer cell lines: Liver [88], various [92], breast [95]; Human cancer cell lines: Liver [88], various [89], breast [90], acute myeloide leukemia [93,94] Anti-tumor role: Murine cancer cell lines: Melanoma [157], plasmacytoma [160]; Human cancer cell line: Colon [156], melanoma [156]
P-Selectin	Metastasis promotion by extravasation into tissue [90,103] Covering of circulating tumor cells in systemic circulation [98,99] Cancer-associated thrombosis [107–109]	Anti-tumor immunity infiltration [157,160]	Pro-tumor role: Murine cancer cell lines: leukemia [103], colon carcinoma [99]; Human cancer cell lines: Breast [90,107], acute lymphoblastic leukemia [103], colon carcinoma [98], various [108,109] Anti-tumor role: Murine cancer cell lines: Melanoma [157], plasmacytoma [160]
L-Selectin	Metastasis promotion by extravasation into tissue [90,103,110,112,113] Dissemination to tissue and lymphatic system [111,114]	Anti-tumor immunity infiltration [157,160] Homing of lymphocytes to lymph nodes [162,163] Synergic effect with immune checkpoint inhibitors [165,166]	Pro-tumor role: Murine cancer cell lines: leukemia [103], insulinoma [111], colon carcinoma [112,113]; Human cancer cell lines: Breast [90,107], acute lymphoblastic leukemia [103,110], various [113], head and neck [114] Anti-tumor role: Murine cancer cell lines: Melanoma [157,165], plasmacytoma [160], breast [162], various [163], chronic infection [166]
ICAM	Metastasis promotion by extravasation into tissue [115–117] Cancer angiogenesis [121–123] Drug resistance (ICAM-3) [132] Immune evasion (ICAM-3) [133]	Anti-tumor immunity infiltration [169–171] Formation of tertiary lymphoid structure [173] Effective target for CAR T-cells [182]	Pro-tumor role: Murine cancer cell lines: Melanoma [115]; Human cancer cell lines: Melanoma [115,117], breast [116,121], colon carcinoma [122], lung [123], various [132], gastric cancer [133] Anti-tumor role: Murine cancer cell lines: virus induced tumors [169], various [170,182]; Human cancer cell line: colon carcinoma [171], breast [173]
VCAM-1	Mediates interaction between cancer cells and tumor associated macrophages [136,139] Metastasis promotion by extravasation into tissue [77,142] Cancer angiogenesis [137]	Anti-tumor immunity infiltration [147,148,187–189] Synergic effect with immune checkpoint inhibitors [191,192]	Pro-tumor role: Murine cancer cell lines: Glioblastoma [139]; Human cancer cell lines: Breast [136], glioblastoma [139], various [77], melanoma [142], gastric cancer [137] Anti-tumor role: Murine cancer cell lines: Melanoma [147,188,189], breast [148], lung [148], various [191]; Human cancer cell line: Colon carcinoma [147], breast [148], pancreatic ductal adenocarcinoma [187], lung [192]

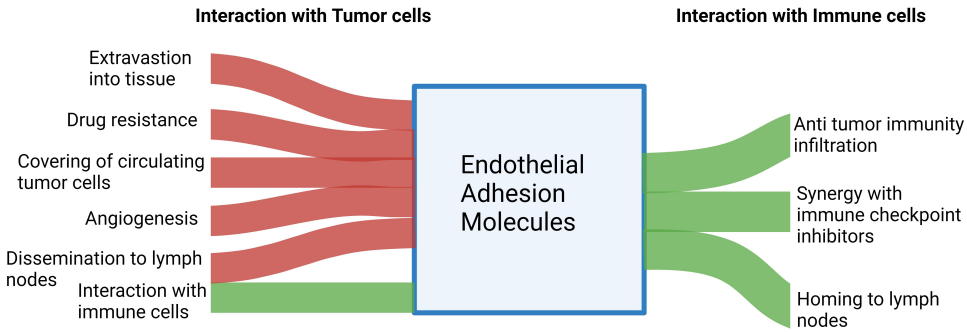


Figure 2. Modified Sankey plot depicting the contribution of endothelial adhesion molecules interaction with tumor cells and immune cells. Positive contributions are represented in green while negative contributions are colored in red.

The impact of ICAM-1 expression seems more ambivalent. When expressed on tumor cells, ICAM-1 harbors a pro-tumoral role and promotes metastasis [118,119]. However, this same tumor expression favors a local response against the tumor by tertiary lymphoid structure formation inside tumors [173,176]. Therefore, its inhibition requires a contextualization of the tumor type and immune microenvironment. Moreover, ICAM-1 is an effective target for tumor inhibition following CTLA-4 abrogation or CAR-T cells treatment [180,183].

Finally, VCAM-1 expression on tumor cells contributes mostly to cancer progression via the recruitment of macrophages and subsequent changes in tumor vasculature favoring cancer cell dissemination [135,139,145]. However, VCAM-1 expression on endothelial cells favors a change in the immune microenvironment promoting T-cell infiltration of tumors and cancer control [187–189].

In conclusion, contribution of adhesion molecules to tumor progression depends on the location of expression, the cancer type and immune microenvironment and potential associated therapies. Further

Table 2. Summary of human studies investigating the prognosis value of adhesion molecules. OS: overall survival, NSCLC, non-small cell lung cancer.

Name of first author	Number of patients	Cancer type	Main finding
Tanio et al. [85]	117	Renal cancer	Membrane expression of functional E-selectin correlated more significantly with poor prognosis of patients
Chien et al. [87]	89	AML	E-selectin ligand expression in blast correlates with lower survival and higher propagation
Aref et al. (2002) [110]	50	AML	Patients with higher soluble E and L selectins levels had shorter event free surviva than patients with lower levels.
Papachristos et al. [122]	46	Colorectal cancer	The ICAM-1 rs1799969 G/A allele was associated with prolonged OS.
Maeda et al. [125]	96	Colorectal cancer	Incidence of lymph node or liver metastasis was significantly lower in patients with ICAM-1-positive tumors
Liu et al. [154]	149	Colorectal cancer	Soluble VCAM-1 was also potentially predictive of lower OS and of benefit from regorafenib
Li et al. [168]	613	Colorectal cancer	SELL expression was associated with favorable outcomes in CRC patients
Dowlati et al. [123]	878	NSCLC	Patients with low baseline soluble ICAM had a higher response rate better overall survival better 1-year survival (65% versus 25%) than those with high ICAM
Carbone et al. [192]	71	NSCLC	High baseline serum levels of VCAM-1 are associated with a longer survival in patients treated with nivolumab as second line treatment for NSCLC
Jung et al. [126]	157	Gastric cancer	Increased expression of intercellular adhesion molecule-1 in gastric cancer could be related to the aggressive nature of the tumor, and has a poor prognostic effect on gastric cancer
Liu et al. [133]	504	Gastric cancer	ICAM-3 expression in tumor is associated with immune evasion
Ding et a.l [137]	41	Gastric cancer	VCAM-1 positive cancers were associated with more lymph node metastases than VCAM-1-negative ones
Byrne et al. [149]	93	Breast cancer	Women who developed early recurrence had higher preoperative levels of serum VCAM-1 than those who remained disease free
Schröeder et al. [127]	169	Breast cancer	ICAM-1 expression in the tumor was associated with a more aggressive tumor phenotype
Kumari et al. [167]	77	Breast cancer	SELL expression is associated with favorable survival outcomes
Bulska-Będkowska et al. [153]	39	Breast cancer	Higher levels of soluble ICAM-1 were associated with faster progression of breast cancer
Mori et al. [151]	1036	Urothelial carcinoma	Preoperative plasma VCAM-1 was significantly elevated in patients with adverse pathologic features. Higher VCAM-1 levels were independently associated with increased risk of lymph-node-metastasis, ≥pT3 disease, and non-organ-confined disease and lower recurrence-free survival, cancer-specific survival, and overall survival (OS) in pre- and postoperative multivariable models
Huang et al. [152]	73	Nasopharyngeal carcinoma	Patients with high VCAM-1 expression were more prone to shorter periods of PFS and OS
Cao et al. [178]	87	Hepatocarcinoma	Patients with elevated level of soluble ICAM-1 showed the lowest TFS and OS but higher immune cells count
Wu et al. [181]	43	Melanoma	Expression of E-selectin and VCAM1 on melanoma tumor-associated endothelial cells promoted adhesion of activated T cells onto endothelial cells

studies in different cancer contexts are required to highlight the contribution of adhesion molecules for cancer control of progression.

Conclusion

The endothelium plays a critical role in tissue homeostasis by regulating their interaction with circulating elements. Adhesion molecules at their surface are hijacked by tumor cells to enter or exit the circulation during the metastasis process. Conversely, these same adhesion molecules are essential for patients to develop an anti-tumor immunity through the recruitment and elaboration of a cytotoxic immune response. Therefore the therapeutic manipulation of adhesion molecules requires attention because of their ambivalent role and should be tailored to the cancer type and its immune microenvironment. Based on this review, a specific focus on expression of L-Selectin and VCAM-1 could have a promising anti-tumoral effect through their capacity to enhance anti-tumor immunity alone or in combination with immunotherapy while not being so involved in cancer cell dissemination. Further research in this field is mandatory.

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Author contributions

Conceptualization, LEC and JYP.; methodology, LEC.; validation, SC and JYP; data curation, LEC.; writing – original draft preparation, LEC, SC and JYP.; writing – review and editing, SC and JYP.; visualization, LEC and

JYP.; supervision, SC and JYP; project administration, LEC and JYP.; funding acquisition, LEC and JYP. All authors have read and agreed to the published version of the manuscript.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

[1] Sobierajska K, Ciszewski WM, Sacewicz-Hofman I, et al. Endothelial cells in the tumor microenvironment. Adv Exp Med Biol. 2020;1234:71–86.

[2] Sturtzel C. Endothelial cells. Adv Exp Med Biol. 2017;1003:71–91.

[3] Opitz B, Eitel J, Meixenberger K, et al. Role of toll-like receptors, nod-like receptors and RIG-I-like receptors in endothelial cells and systemic infections. Thromb Haemost. 2009;102(12):1103–1109. doi: 10.1160/TH09-05-0323

[4] Kreuger J, Phillipson M. Targeting vascular and leukocyte communication in angiogenesis, inflammation and fibrosis. Nat Rev Drug Discov. 2016;15(2):125. doi: 10.1038/nrd.2015.2

[5] Moreira MB, Garcia-Cardeña G, Saffi MA, et al. Endothelium: a coordinator of acute and chronic inflammation. Endothelium and cardiovascular diseases: vascular biology and clinical syndromes. Amsterdam, Netherlands: Elsevier; 2018. p. 485–491.

[6] British Thoracic Society Standards of Care Committee. BTS statement on malignant mesothelioma in the UK. Thorax. 2007 Nov;62 Suppl 2(Suppl 2):ii1–ii19.

[7] Baas P, Fennell D, Kerr KM, et al. ESMO guidelines committee. Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v31–v39. doi: 10.1093/annonc/mdv199

[8] Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021;397 (10272):375–386. doi: 10.1016/S0140-6736(20)32714-8

[9] Bevilacqua MP, Stengelin S, Gimbrone MA, et al. Endothelial leukocyte adhesion molecule 1: an inducible receptor for neutrophils related to complement regulatory proteins and lectins. Science. 1989;243 (4895):1160–1165. doi: 10.1126/science.2466335

[10] Johnston GI, Cook RG, McEver RP. Cloning of GMP-140, a granule membrane protein of platelets and endothelium: sequence similarity to proteins involved in cell adhesion and inflammation. Cell. 1989;56 (6):1033–1044. doi: 10.1016/0092-8674(89)90636-3

[11] Siegelman MH, van de Rijn M, Weissman IL. Mouse lymph node homing receptor cDNA clone encodes a glycoprotein revealing tandem interaction domains. Science. 1989;243(4895):1165–1172. doi: 10.1126/science.2646713

[12] Lasky A, Singer MS, Yednock TA, et al. Cloning of a lymphocyte homing receptor reveals a lectin domain. Cell. 1989;56(6):1045–1055. doi: 10.1016/0092-8674(89)90637-5

[13] Bevilacqua M. Endothelial-leukocyte adhesion molecules. Annu Rev Immunol. 1993;11(1):767–804. doi: 10.1146/annurev.iy.11.040193.004003

[14] Larsen E, Celi A, Gilbert GE, et al. PADGEM protein: a receptor that mediates the interaction of activated platelets with neutrophils and monocytes. Cell. 1989;59 (2):305–312. doi: 10.1016/0092-8674(89)90292-4

[15] Geng J-G, Bevilacquat MP, Moore KL, et al. Rapid neutrophil adhesion to activated endothelium mediated by GMP-140. Nature. 1990;343 (6260):757–760. doi: 10.1038/343757a0

[16] Varki A. Selectin ligands. Proc Natl Acad Sci USA. 1994;91(16):7390–7397. doi: 10.1073/pnas.91.16.7390

[17] Bevilacqua M, Pober JS, Wheeler ME. Interleukin 1 acts on cultured human vascular endothelium to increase the adhesion of polymorphonuclear leukocytes, monocytes, and related leukocyte cell lines. J Clin Invest. 1985;76(5):2003–2011. doi: 10.1172/JCI112200

[18] Gamble JR, Harlan JM, Klebanoff SJ, et al. Stimulation of the adherence of neutrophils to umbilical vein endothelium by human recombinant tumor necrosis factor. Proc Natl Acad Sci USA. 1985;82 (24):8667–8671. doi: 10.1073/pnas.82.24.8667

[19] Graber N, Gopal TV, Wilson D, et al. T cells bind to cytokine-activated endothelial cells via a novel, inducible sialoglycoprotein and endothelial leukocyte adhesion molecule-1. J Immunol. 1990;145 (3):819–830. doi: 10.4049/jimmunol.145.3.819

[20] Shimizu Y, Shaw S, Graber N, et al. Activation-independent binding of human memory T cells to adhesion molecule ELAM-1. Nature. 1991;349 (6312):799–802. doi: 10.1038/349799a0

[21] Hakkert BC, Kuijpers TW, Leeuwenberg JF, et al. Neutrophil and monocyte adherence to and migration across mono layers of cytokine-activated endothelial cells: the contribution of CD18, elam-l, VLA-4. Blood. 1991;78(10):2721–2726. doi: 10.1182/blood.V78.10.2721.2721

[22] El Berg EL, Robinson MK, Mansson O, et al. A carbohydrate domain common to both sialyl Le(a) and sialyl Le(X) is recognized by the endothelial cell leukocyte adhesion molecule ELAM-1. J Biol Chem. 1991;266 (23):14869–14872. doi: 10.1016/S0021-9258(18)98555-8

[23] Bonfanti R, Furie BC, Furie B, et al. PADGEM (GMP140) is a component of Weibel-palade bodies of human endothelial cells. Blood. 1989;73 (5):1109–1112. doi: 10.1182/blood.V73.5.1109.1109

[24] McEver RP, Beckstead JH, Moore KL, et al. GMP-140, a platelet alpha-granule membrane protein, is also synthesized by vascular endothelial cells and is localized in Weibel-Palade bodies. J Clin Invest. 1989;84 (1):92–99. doi: 10.1172/JCI114175

[25] Hamburger A, McEver RP. GMP-140 mediates adhesion of stimulated platelets to neutrophils. Blood. 1990;75(3):550–554. doi: 10.1182/blood.V75.3.550.550

[26] Chao CC, Jensen R, Dailey MO. Mechanisms of L-selectin regulation by activated T cells. J Immunol. 1997;159 (4):1686–1694. doi: 10.4049/jimmunol.159.4.1686

[27] Jung TM, Gallatin WM, Weissman IL, et al. Down-regulation of homing receptors after T cell activation.

J Immunol. 1988;141(12):4110–4117. doi: 10.4049/jimmunol.141.12.4110

[28] Rosen S. Ligands for L-selectin: homing, inflammation, and beyond. Annu Rev Immunol. 2004;22(1):129–156. doi: 10.1146/annurev.immunol.21.090501.080131

[29] Shimizu Y, Newman W, Tanaka Y. Lymphocyte interactions with endothelial cells. Immunol Today. 1992;13(3):106–112. doi: 10.1016/0167-5699(92)90151-V

[30] Picker LJ, Butcher EC. Physiological and molecular mechanisms of lymphocyte homing. Annu Rev Immunol. 1992;10(1):561–591. doi: 10.1146/annurev.iy.10.040192.003021

[31] Simmons D, Makgoba MW, Seed B. ICAM, an adhesion ligand of LFA-1, is homologous to the neural cell adhesion molecule NCAM. Nature. 1988;331(6157):624–627. doi: 10.1038/331624a0

[32] Staunton DE, Marlin SD, Stratowa C, et al. Primary structure of ICAM-1 demonstrates interaction between members of the immunoglobulin and integrin supergene families. Cell. 1988;52(6):925–933. doi: 10.1016/0092-8674(88)90434-5

[33] Staunton DE, Hakkert BC, Hoogerwerf M. Role of endothelial leukocyte adhesion molecule-1 and platelet-activating factor in neutrophil adherence to IL-1-prestimulated endothelial cells. Endothelial leukocyte adhesion molecule-1-mediated CD18 activation. J Immunol. 1989;147(4):1369–1376. doi: 10.4049/jimmunol.147.4.1369

[34] Tan S-M. The leucocyte β2 (CD18) integrins: the structure, functional regulation and signalling properties. Biosci Rep. 2012;32(3):241–269. doi: 10.1042/BSR20110101

[35] Schittenhelm L, Hilkens CM, Morrison VL. β2 Integrins as regulators of dendritic cell, monocyte, and macrophage function. Front Immunol. 2017;8(8):1866. doi: 10.3389/fimmu.2017.01866

[36] Fagerholm SC, Guenther C, Llort Asens M, et al. Beta2-integrins and interacting proteins in leukocyte trafficking, immune suppression, and immunodeficiency disease. Front Immunol. 2019;10(10):254. doi: 10.3389/fimmu.2019.00254

[37] Hubbard A, Rothlein R. Intercellular adhesion molecule-1 (ICAM-1) expression and cell signaling cascades. Free Radical Biol Med. 2000;28(9):1379–1386. doi: 10.1016/S0891-5849(00)00223-9

[38] Wee H, Oh H-M, Jo J-H, et al. ICAM-1/LFA-1 interaction contributes to the induction of endothelial cell-cell separation: implication for enhanced leukocyte diapedesis. Exp Mol Med. 2009;41(5):341–348. doi: 10.3858/emm.2009.41.5.038

[39] Gorina R, Lyck R, Vestweber D, et al. β2 integrin–mediated crawling on endothelial ICAM-1 and ICAM-2 is a prerequisite for transcellular neutrophil diapedesis across the inflamed blood–brain barrier. J Immunol. 2014;192(1):324–337. doi: 10.4049/jimmunol.1300858

[40] Rothlein R, Dustin ML, Marlin SD, et al. A human intercellular adhesion molecule (ICAM-1) distinct from LFA-1. J Immunol. 1986;137(4):1270–1274. doi: 10.4049/jimmunol.137.4.1270

[41] Bui TM, Wiesolek HL, Sumagin R. ICAM-1: a master regulator of cellular responses in inflammation, injury resolution, and tumorigenesis. J Leukoc Biol. 2020;108(3):787–799. doi: 10.1002/JLB.2MR0220-549R

[42] Grakoui A, Bromley SK, Sumen C, et al. The immunological synapse: a molecular machine controlling T cell activation. Science. 1999 Jul 9;285(5425):221–227. doi: 10.1126/science.285.5425.221

[43] Krummel MF, Davis MM. Dynamics of the immunological synapse: finding, establishing and solidifying a connection. Curr Opin Immunol. 2002 Feb;14(1):66–74. doi: 10.1016/S0952-7915(01)00299-0

[44] Dustin ML, Rothlein R, Bhan AK, et al. Induction by IL 1 and interferon-gamma: tissue distribution, biochemistry, and function of a natural adherence molecule (ICAM-1). J Immunol. 1986;137(1):245–254. doi: 10.4049/jimmunol.137.1.245

[45] Pober JS, Gimbrone MA, Lapierre LA, et al. Overlapping patterns of activation of human endothelial cells by interleukin 1, tumor necrosis factor, and immune interferon. J Immunol. 1986;137(6):1893–1896. doi: 10.4049/jimmunol.137.6.1893

[46] Nortamo P, Li R, Renkonen R, et al. The expression of human intercellular adhesion molecule-2 is refractory to inflammatory cytokines. Eur J Immunol. 1991;21(10):2629–2632. doi: 10.1002/eji.1830211049

[47] Staunton DE, Dustin ML, Springer TA. Functional cloning of ICAM-2, a cell adhesion ligand for LFA-1 homologous to ICAM-1. Nature. 1989;339(6219):61–64. doi: 10.1038/339061a0

[48] Huang M-T, Mason JC, Birdsey GM, et al. Endothelial intercellular adhesion molecule (ICAM)–2 regulates angiogenesis. Blood. 2005;106(5):1636–1643. doi: 10.1182/blood-2004-12-4716

[49] Xie J, Li R, Kotovuori P, et al. Intercellular adhesion molecule-2 (CD102) binds to the leukocyte integrin CD11b/CD18 through the a domain. J Immunol. 1995;155(7):3619–3628. doi: 10.4049/jimmunol.155.7.3619

[50] Huang M-T, Larbi KY, Scheiermann C, et al. ICAM-2 mediates neutrophil transmigration in vivo: evidence for stimulus specificity and a role in PECAM-1–independent transmigration. Blood. 2006;107(12):4721–4727. doi: 10.1182/blood-2005-11-4683

[51] Amsellem V, Dryden NH, Martinelli R, et al. ICAM-2 regulates vascular permeability and N-cadherin localization through Ezrin-radixin-moesin (ERM) proteins and rac-1 signalling. Cell Commun Signal. 2014;12(1):12. doi: 10.1186/1478-811X-12-12

[52] Geijtenbeek TBH, Krooshoop DJEB, Bleijs DA, et al. DC-SIGN–ICAM-2 interaction mediates dendritic cell trafficking. Nat Immunol. 2000;1(4):353–357. doi: 10.1038/79815

[53] de Fougerolles A, Stacker SA, Schwarting SA, et al. Characterization of ICAM-2 and evidence for a third counter-receptor for LFA-1. J Exp Med. 1991;174(1):253–267. doi: 10.1084/jem.174.1.253

[54] de Fougerolles, Springer TA, de Fougerolles AR. Intercellular adhesion molecule 3, a third adhesion counter-receptor for lymphocyte function-associated molecule 1 on resting lymphocytes. J Exp Med. 1992;175(1):185–190. doi: 10.1084/jem.175.1.185

[55] Hernandez-Caselles T, Rubio G, Campanero MR, et al. ICAM-3, the third LFA-1 counterreceptor, is a

co-stimulatory molecule for both resting and activated T lymphocytes. Eur J Immunol. 1993;23 (11):2799–2806. doi: 10.1002/eji.1830231112

[56] Campanero MR, Del Pozo MA, Arroyo AG, et al. ICAM-3 interacts with LFA-1 and regulates the LFA-1/ICAM-1 cell adhesion pathway. J Cell Biol. 1993;123(4):1007–1016. doi: 10.1083/jcb.123.4.1007

[57] Juan M, Viñas O, Pino-Otín MR, et al. CD50 (intercellular adhesion molecule 3) stimulation induces calcium mobilization and tyrosine phosphorylation through p59fyn and p56lck in Jurkat T cell line. J Exp Med. 1994;179(6):1747–1756. doi: 10.1084/jem.179.6.1747

[58] Bleijs A, de Waal-Malefyt R, Figdor CG, et al. Co-stimulation of T cells results in distinct IL-10 and tnf-α cytokine profiles dependent on binding to ICAM-1, ICAM-2 or ICAM-3. Eur J Immunol. 1999;29 (7):2248–2258. doi: 10.1002/(SICI)1521-4141(199907)29:07<2248::AID-IMMU2248>3.0.CO;2-9

[59] Montoya MC, Sancho D, Bonello G, et al. Role of ICAM-3 in the initial interaction of T lymphocytes and APCs. Nat Immunol. 2002;3(2):159–168. doi: 10.1038/ni753

[60] Gahmberg CG, Jokinen M, Andersson LC. Expression of the major sialoglycoprotein (glycophorin) on erythroid cells in human bone marrow. Blood. 1978;52 (2):379–387. doi: 10.1182/blood.V52.2.379.379

[61] Spring A, Parsons SF, Ortlepp S, et al. Intercellular adhesion molecule-4 binds α4β1 and αV-family integrins through novel integrin-binding mechanisms. Blood. 2001;98(2):458–466. doi: 10.1182/blood.V98.2.458

[62] Hermand P, Gane P, Callebaut I, et al. Integrin receptor specificity for human red cell ICAM-4 ligand. Critical residues for alphaIibeta3 binding. Eur J Biochem. 2004;271(18):3729–3740. doi: 10.1111/j.1432-1033.2004.04313.x

[63] Hermand P, Gane P, Huet M, et al. Red cell ICAM-4 is a novel ligand for platelet-activated αIIbβ3 integrin. J Biol Chem. 2003;278(7):4892–4898. doi: 10.1074/jbc.M211282200

[64] Gahmberg C. Cell adhesion: a partner for many. Blood. 2004;103(4):1183. doi: 10.1182/blood-2003-12-4113

[65] Ihanus E, Uotila LM, Toivanen A, et al. Red-cell ICAM-4 is a ligand for the monocyte/macrophage integrin CD11c/CD18: characterization of the binding sites on ICAM-4. Blood. 2007;109(2):802–810. doi: 10.1182/blood-2006-04-014878

[66] Yang H. Structure, expression, and function of ICAM-5. Comp Funct Genomics. 2012;2012:1–11. doi: 10.1155/2012/368938

[67] Mizuno T, Yoshihara Y, Inazawa J, et al. cDNA cloning and chromosomal localization of the human telencephalin and its distinctive interaction with lymphocyte function-associated antigen-1. J Biol Chem. 1997;272(2):1156–1163. doi: 10.1074/jbc.272.2.1156

[68] Springer A. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. Cell. 1994;76(2):301–314. doi: 10.1016/0092-8674(94)90337-9

[69] Tian L, Yoshihara Y, Mizuno T, et al. The neuronal glycoprotein telencephalin is a cellular ligand for the CD11a/CD18 leukocyte integrin. J Immunol. 1997;158 (2):928–936. doi: 10.4049/jimmunol.158.2.928

[70] Mizuno T, Yoshihara Y, Kagamiyama H, et al. Neuronal adhesion molecule telencephalin induces rapid cell spreading of microglia. Brain Res. 1999;849(1–2):58–66. doi: 10.1016/S0006-8993(99)01984-8

[71] Wakabayashi Y, Tsujimura A, Matsuda K-I, et al. Appearance of LFA-1 in the initial stage of synaptogenesis of developing hippocampal neurons. Arch Histol Cytol. 2008;71(1):23–36. doi: 10.1679/aohc.71.23

[72] Tse Margaret CL, Lane C, Mott K, et al. ICAM-5 modulates cytokine/chemokine production in the CNS during the course of herpes simplex virus type 1 infection. J Neuroimmunol. 2009;213(1–2):12–19. doi: 10.1016/j.jneuroim.2009.06.007

[73] Cook-Mills JM, Marchese ME, Abdala-Valencia H. Vascular cell adhesion molecule-1 expression and signaling during disease: regulation by reactive oxygen species and antioxidants. Antioxid Redox Signal. 2011;15(6):1607–1638. doi: 10.1089/ars.2010.3522

[74] Rice GE, Bevilacqua MP. An inducible endothelial cell surface glycoprotein mediates melanoma adhesion. Science. 1989;246(4935):1303–1306. doi: 10.1126/science.2588007

[75] Sharma R, Sharma R, Khaket TP, et al. Breast cancer metastasis: putative therapeutic role of vascular cell adhesion molecule-1. Cell Oncol. 2017;40(3):199–208. doi: 10.1007/s13402-017-0324-x

[76] Van Oosten M, van de Bilt E, de Vries HE, et al. Vascular adhesion molecule-1 and intercellular adhesion molecule-1 expression on rat liver cells after lipopolysaccharide administration in vivo. Hepatology. 1995;22(5):1538–1546. doi: 10.1002/hep.1840220529

[77] Kong D-H, Kim Y, Kim M, et al. Emerging roles of vascular cell adhesion molecule-1 (VCAM-1) in immunological disorders and cancer. Int J Mol Sci. 2018;19(4):1057. doi: 10.3390/ijms19041057

[78] Cerutti C, Ridley AJ. Endothelial cell-cell adhesion and signaling. Exp Cell Res. 2017;358(1):31–38. doi: 10.1016/j.yexcr.2017.06.003

[79] Pober JS. Endothelial activation: intracellular signaling pathways. Arthritis Res. 2002;4(Suppl S3):S109–S116. doi: 10.1186/ar576

[80] Witz IP. The selectin–selectin ligand axis in tumor progression. Cancer Metastasis Rev. 2008;27 (1):19–30. doi: 10.1007/s10555-007-9101-z

[81] Burdick MM, Henson KA, Delgadillo LF, et al. Expression of E-selectin ligands on circulating tumor cells: cross-regulation with cancer stem cell regulatory pathways? Front Oncol. 2012;2:10. doi: 10.3389/fonc.2012.00103

[82] Kannagi R, Izawa M, Koike T, et al. Carbohydrate-mediated cell adhesion in cancer metastasis and angiogenesis. Cancer Sci. 2004;95(5):377–384. doi: 10.1111/j.1349-7006.2004.tb03219.x

[83] Borsig A, Stevenson JL, Varki A. Cancer Associated Thrombosis. 1st ed. Boca Raton, Florida, United-States: CRC Press; 2007. p. 97–113.

[84] Kim YJ, Varki A. Perspectives on the significance of altered glycosylation of glycoproteins in cancer. Glycoconj J. 1997;14(5):569–576. doi: 10.1023/A:1018580324971

[85] Tanio M, Muramoto A, Hoshino H, et al. Expression of functional E-selectin ligands on the plasma membrane of carcinoma cells correlates with poor prognosis in clear cell renal cell carcinoma. Urol Oncol. 2021;39(5):.e302.9–.e302.18. doi: 10.1016/j.urolonc.2021.02.013

[86] Natoni A, Smith TAG, Keane N, et al. E-selectin ligands recognised by HECA452 induce drug resistance in myeloma, which is overcome by the E-selectin antagonist, GMI-1271. Leukemia. 2017;31(12):2642–2651. doi: 10.1038/leu.2017.123

[87] Chien SS, Dai J, Magnani JL, et al. E-Selectin ligand expression by leukemic blasts is associated with prognosis in patients with AML. Blood. 2018;132(Supplement 1):1513. doi: 10.1182/blood-2018-99-119449

[88] Brodt P, Fallavollita L, Bresalier RS, et al. Liver endothelial E-selectin mediates carcinoma cell adhesion and promotes liver metastasis. Int J Cancer. 1997;71(4):612–619. doi: 10.1002/(SICI)1097-0215(19970516)71:4<612::AID-IJC17>3.0.CO;2-D

[89] Lange T, Valentiner U, Wicklein D, et al. Tumor cell E-selectin ligands determine partial efficacy of bortezomib on spontaneous lung metastasis formation of solid human tumors in vivo. Mol Ther. 2022;30(4):1536–1552. doi: 10.1016/j.ymthe.2022.01.017

[90] Khan SU, Xia Y, Goodale D, et al. Lung-derived selectins enhance metastatic behavior of triple negative breast cancer cells. Biomedicines. 2021;9(11):1580. doi: 10.3390/biomedicines9111580

[91] Coppo R, Orso F, Virga F, et al. ESDN inhibits melanoma progression by blocking E-selectin expression in endothelial cells via STAT3. Cancer Lett. 2021;510(510):13–23. doi: 10.1016/j.canlet.2021.04.005

[92] Winkler IG, Barbier V, Nowlan B, et al. Vascular niche E-selectin regulates hematopoietic stem cell dormancy, self renewal and chemoresistance. Nat Med. 2012;18(11):1651–1657. doi: 10.1038/nm.2969

[93] Chien S, Haq SU, Pawlus M, et al. Adhesion of acute myeloid leukemia blasts to E-Selectin in the vascular niche enhances their survival by mechanisms such as wnt activation. Blood. 2013;122(21):61. doi: 10.1182/blood.V122.21.61.61

[94] Barbier V, Erbani J, Fiveash C, et al. Endothelial E-selectin inhibition improves acute myeloid leukaemia therapy by disrupting vascular niche-mediated chemoresistance. Nat Commun. 2020;11(1):2042. doi: 10.1038/s41467-020-15817-5

[95] Morita Y, Leslie M, Kameyama H, et al. Functional blockade of E-Selectin in tumor-associated vessels enhances anti-tumor effect of doxorubicin in breast cancer. Cancers (Basel). 2020;12(3):725. doi: 10.3390/cancers12030725

[96] Strasenburg W, Jóźwicki J, Durślewicz J, et al. Tumor cell-induced platelet aggregation as an emerging therapeutic target for cancer therapy. Front Oncol. 2022;12(12):909767. doi: 10.3389/fonc.2022.909767

[97] Kim YJ, Borsig L, Varki NM, et al. P-selectin deficiency attenuates tumor growth and metastasis. Proc Natl Acad Sci USA. 1998;95(16):9325–9330. doi: 10.1073/pnas.95.16.9325

[98] Borsig L, Wong R, Feramisco J, et al. Heparin and cancer revisited: mechanistic connections involving platelets, P-selectin, carcinoma mucins, and tumor metastasis. Proc Natl Acad Sci USA. 2001;98(6):3352–3357. doi: 10.1073/pnas.061615598

[99] Borsig L, Wong R, Hynes RO, et al. Synergistic effects of L- and P-selectin in facilitating tumor metastasis can involve non-mucin ligands and implicate leukocytes as enhancers of metastasis. Proc Natl Acad Sci USA. 2002;99(4):2193–2198. doi: 10.1073/pnas.261704098

[100] Mannori G, Crottet P, Cecconi O, et al. Differential colon cancer cell adhesion to E-, P-, and L-selectin: role of mucin-type glycoproteins. Cancer Res. 1995;55(19):4425–4431.

[101] Häuselmann I, Borsig L. Altered tumor-cell glycosylation promotes metastasis. Front Oncol. 2014;4(4):28. doi: 10.3389/fonc.2014.00028

[102] Cariello M, Piccinin E, Zerlotin R, et al. Adhesion of platelets to colon cancer cells is necessary to promote tumor development in xenograft, genetic and inflammation models. Cancers (Basel). 2021;13(16):4243. doi: 10.3390/cancers13164243

[103] Pereira JL, Cavaco P, da Silva RC, et al. P-selectin glycoprotein ligand 1 promotes T cell lymphoma development and dissemination. Transl Oncol. 2021;14(8):101125. doi: 10.1016/j.tranon.2021.101125

[104] Azab A, Quang P, Azab F, et al. P-selectin glycoprotein ligand regulates the interaction of multiple myeloma cells with the bone marrow microenvironment. Blood. 2012;119(6):1468–1478. doi: 10.1182/blood-2011-07-368050

[105] Zhang R, Guo H, Xu J, et al. Activated platelets inhibit hepatocellular carcinoma cell differentiation and promote tumor progression via platelet-tumor cell binding. Oncotarget. 2016;7(37):60609–60622. doi: 10.18632/oncotarget.11300

[106] Kim J, Sunkara V, Kim J, et al. Prediction of tumor metastasis via extracellular vesicles-treated platelet adhesion on a blood vessel chip. Lab Chip. 2022;22(14):2726–2740. doi: 10.1039/D2LC00364C

[107] Gomes FG, Sandim V, Almeida VH, et al. Breast-cancer extracellular vesicles induce platelet activation and aggregation by tissue factor-independent and -dependent mechanisms. Thromb Res. 2017;159:24–32. doi: 10.1016/j.thromres.2017.09.019

[108] Yeini E, Satchi-Fainaro R. The role of P-selectin in cancer-associated thrombosis and beyond. Thromb Res. 2022;213(Suppl 1):S22–S28. doi: 10.1016/j.thromres.2021.12.027

[109] Almeida VH, Rondon AMR, Gomes T, et al. Novel aspects of extracellular vesicles as mediators of cancer-associated thrombosis. Cells. 2019;8(7):716. doi: 10.3390/cells8070716

[110] Aref S, Salama O, Al-Tonbary Y, et al. L and E selectins in acute myeloid leukemia: expression, clinical relevance and relation to patient outcome. Hematology. 2002;7(2):83–87. doi: 10.1080/10245330290028579

[111] Qian F, Hanahan D, Weissman IL. L-selectin can facilitate metastasis to lymph nodes in a transgenic

mouse model of carcinogenesis. Proc Natl Acad Sci USA. 2001;98(7):3976–3981. doi: 10.1073/pnas.061633698

[112] Läubli H, Stevenson JL, Varki A, et al. L-selectin facilitation of metastasis involves temporal induction of Fut7-dependent ligands at sites of tumor cell arrest. Cancer Res. 2006;66(3):1536–1542. doi: 10.1158/0008-5472.CAN-05-3121

[113] Läubli H, Spanaus K-S, Borsig L. Selectin-mediated activation of endothelial cells induces expression of CCL5 and promotes metastasis through recruitment of monocytes. Blood. 2009 Nov 12;114(20):4583–4591. doi: 10.1182/blood-2008-10-186585

[114] Resto A, Burdick MM, Dagia NM, et al. L-selectin-mediated lymphocyte-cancer cell interactions under low fluid shear conditions. J Biol Chem. 2008 Jun 6;283(23):15816–15824. doi: 10.1074/jbc.M708899200

[115] Ghislin S, Obino D, Middendorp S, et al. LFA-1 and ICAM-1 expression induced during melanoma-endothelial cell co-culture favors the transendothelial migration of melanoma cell lines in vitro. BMC Cancer. 2012;12(1):455. doi: 10.1186/1471-2407-12-455

[116] Di D, Chen L, Wang L, et al. Downregulation of human intercellular adhesion molecule-1 attenuates the metastatic ability in human breast cancer cell lines. Oncol Rep. 2016;35(3):1541–1548. doi: 10.3892/or.2016.4543

[117] Hamaï A, Meslin F, Benlalam H, et al. ICAM-1 has a critical role in the regulation of metastatic melanoma tumor susceptibility to CTL lysis by interfering with PI3K/AKT pathway. Cancer Res. 2008;68(23):9854–9864. doi: 10.1158/0008-5472.CAN-08-0719

[118] Chen A, Wu C, Fu Z. ICAM1 promotes bone metastasis via integrin-mediated tgf-β/EMT signaling in triple-negative breast cancer. Cancer Sci. 2022;113(11):3751–3765.

[119] Taftaf R, Liu X, Singh S, et al. ICAM1 initiates CTC cluster formation and trans-endothelial migration in lung metastasis of breast cancer. Nat Commun. 2021;12(1):4867. doi: 10.1038/s41467-021-25189-z

[120] Kong J, Yao C, Dong S, et al. ICAM-1 activates platelets and promotes endothelial permeability through VE-Cadherin after insufficient radiofrequency ablation. Adv Sci. 2021;8(4):2002228. doi: 10.1002/advs.202002228

[121] Guo P, Yang J, Jia D, et al. ICAM-1-Targeted, Lcn2 siRNA-encapsulating liposomes are potent anti-angiogenic agents for triple negative breast cancer. Theranostic. 2016;6(1):1–13. doi: 10.7150/thno.12167

[122] Papachristos A, Kemos P, Katsila T, et al. Vegf-A and ICAM-1 gene polymorphisms as predictors of clinical outcome to first-line bevacizumab-based treatment in metastatic colorectal cancer. Int J Mol Sci. 2019;20(22):5791. doi: 10.3390/ijms20225791

[123] Dowlati A, Gray R, Sandler AB, et al. Cell adhesion molecules, vascular endothelial growth factor, and basic fibroblast growth factor in patients with non–Small cell lung cancer treated with chemotherapy with or without Bevacizumab—an eastern cooperative oncology group study. Clin Cancer Res. 2008;14(5):1407–1412. doi: 10.1158/1078-0432.CCR-07-1154

[124] Usami Y, Ishida K, Sato S, et al. Intercellular adhesion molecule-1 (ICAM-1) expression correlates with oral cancer progression and induces macrophage/cancer cell adhesion. Intl J Cancer. 2013;133(3):568–578. doi: 10.1002/ijc.28066

[125] Maeda K, Kang S-M, Sawada T, et al. Expression of intercellular adhesion molecule-1 and prognosis in colorectal cancer. Oncol Rep. 2002;9(3):511–514. doi: 10.3892/or.9.3.511

[126] Jung W-C, Jang Y-J, Kim J-H, et al. Expression of intercellular adhesion molecule-1 and e-selectin in gastric cancer and their clinical significance. J Gastric Cancer. 2012;12(3):140–148. doi: 10.5230/jgc.2012.12.3.140

[127] Schröder C, Witzel I, Müller V, et al. Prognostic value of intercellular adhesion molecule (ICAM)-1 expression in breast cancer. J Cancer Res Clin Oncol. 2011;137(8):1193–1201. doi: 10.1007/s00432-011-0984-2

[128] Melero I, Gabari I, Corbí AL, et al. An anti-ICAM-2 (CD102) monoclonal antibody induces immune-mediated regressions of transplanted ICAM-2-negative colon carcinomas. Cancer Res. 2002;62(11):3167–3174.

[129] Kim Y, Kim M, Lim J, et al. ICAM-3-induced cancer cell proliferation through the PI3K/Akt pathway. Cancer Lett. 2006;239(1):103–110. doi: 10.1016/j.canlet.2005.07.023

[130] Park P, Park SH, So K, et al. ICAM-3 enhances the migratory and invasive potential of human non-small cell lung cancer cells by inducing MMP-2 and MMP-9 via akt and CREB. Int J Oncol. 2010;36(1):181–192. doi: 10.3892/ijo_00000489

[131] Ahn K-C, Choi JY, Kim J-S, et al. ICAM-3 endows anticancer drug resistance against microtubule-damaging agents via activation of the ICAM-3-AKT/ERK-CREB-2 pathway and blockage of apoptosis. Biochem Biophys Res Commun. 2013;441(2):507–513. doi: 10.1016/j.bbrc.2013.10.096

[132] Chung YM, Kim B-G, Park C-S, et al. Increased expression of ICAM-3 is associated with radiation resistance in cervical cancer. Intl J Cancer. 2005;117(2):194–201. doi: 10.1002/ijc.21180

[133] Liu X, Cao Y, Li R, et al. Poor clinical outcomes of intratumoral dendritic cell–specific intercellular adhesion molecule 3–grabbing non-integrin–positive macrophages associated with immune evasion in gastric cancer. Eur J Cancer. 2020;128:27–37. doi: 10.1016/j.ejca.2020.01.002

[134] Maruya SI, Myers JN, Weber RS, et al. ICAM-5 (telencephalin) gene expression in head and neck squamous carcinoma tumorigenesis and perineural invasion! Oral Oncol. 2005;41(6):580–588. doi: 10.1016/j.oraloncology.2005.01.002

[135] Ye H, Zhou Q, Zheng S, et al. Tumor-associated macrophages promote progression and the Warburg effect via CCL18/NF-kB/VCAM-1 pathway in pancreatic ductal adenocarcinoma. Cell Death Dis. 2018;9(5):453. doi: 10.1038/s41419-018-0486-0

[136] Chen Q, Zhang X-F, Massagué J. Macrophage binding to receptor VCAM-1 transmits survival signals in breast cancer cells that invade the lungs. Cancer Cell. 2011;20(4):538–549. doi: 10.1016/j.ccr.2011.08.025

[137] Ding Y-B, Chen GY, Xia JG, et al. Association of VCAM-1 overexpression with oncogenesis, tumor angiogenesis and metastasis of gastric carcinoma. World J Gastroenterol. 2003;9(7):1409–1414. doi: 10.3748/wjg.v9.i7.1409

[138] Schlesinger M, Bendas G. Vascular cell adhesion molecule-1 (VCAM-1)—an increasing insight into its role in tumorigenicity and metastasis. Intl J Cancer. 2015;136(11):2504–2514. doi: 10.1002/ijc.28927

[139] Shen C-K, Huang B-R, Yeh W-L, et al. Regulatory effects of IL-1β in the interaction of GBM and tumor-associated monocyte through VCAM-1 and ICAM-1. Eur J Pharmacol. 2021;905(905):174216. doi: 10.1016/j.ejphar.2021.174216

[140] Lee C-W, Chiang Y-C, Yu P-A, et al. A role of CXCL1 drives osteosarcoma lung metastasis via VCAM-1 production. Front Oncol. 2021;11(11):735277. doi: 10.3389/fonc.2021.735277

[141] Liu J-F, Lee C-W, Lin C-Y, et al. CXCL13/CXCR5 interaction facilitates VCAM-1-Dependent migration in human osteosarcoma. Int J Mol Sci. 2020;21(17):6095. doi: 10.3390/ijms21176095

[142] Klemke M, Weschenfelder T, Konstandin MH, et al. High affinity interaction of integrin α4β1 (VLA-4) and vascular cell adhesion molecule 1 (VCAM-1) enhances migration of human melanoma cells across activated endothelial cell layers. J Cell Physiol. 2007;212(2):368–374. doi: 10.1002/jcp.21029

[143] Sikpa D, Whittingstall L, Fouquet JP, et al. Cerebrovascular inflammation promotes the formation of brain metastases. Intl J Cancer. 2020;147(1):244–255. doi: 10.1002/ijc.32902

[144] Dieterich LC, Kapaklikaya K, Cetintas T, et al. Transcriptional profiling of breast cancer-associated lymphatic vessels reveals VCAM-1 as regulator of lymphatic invasion and permeability. Intl J Cancer. 2019;145(10):2804–2815. doi: 10.1002/ijc.32594

[145] Zhang S, Xie B, Wang L, et al. Macrophage-mediated vascular permeability via VLA4/VCAM1 pathway dictates ascites development in ovarian cancer. J Clin Invest. 2021;131(3):e140315. doi: 10.1172/JCI140315

[146] Zhou Z, Zhou Q, Wu X, et al. VCAM-1 secreted from cancer-associated fibroblasts enhances the growth and invasion of lung cancer cells through AKT and MAPK signaling. Cancer Lett. 2020;473:62–73. doi: 10.1016/j.canlet.2019.12.039

[147] Dirkx A, Oude Egbrink MGA, Kuijpers MJE, et al. Tumor angiogenesis modulates leukocyte-vessel wall interactions in vivo by reducing endothelial adhesion molecule expression. Cancer Res. 2003;63(9):2322–2329.

[148] Delfortrie S, Pinte S, Mattot V, et al. Egfl7 promotes tumor escape from immunity by repressing endothelial cell activation. Cancer Res. 2011;71(23):7176–7186. doi: 10.1158/0008-5472.CAN-11-1301

[149] Byrne GJ, Ghellal A, Iddon J, et al. Serum soluble vascular cell adhesion molecule-1: role as a surrogate marker of angiogenesis. J Natl Cancer Inst. 2000;92(16):1329–1336. doi: 10.1093/jnci/92.16.1329

[150] Sano M, Takahashi R, Ijichi H, et al. Blocking VCAM-1 inhibits pancreatic tumour progression and cancer-associated thrombosis/thromboembolism. Gut. 2021;70(9):1713–1723. doi: 10.1136/gutjnl-2020-320608

[151] Mori K, Schuettfort VM, Katayama S, et al. Prognostic role of preoperative vascular cell adhesion molecule-1 plasma levels in urothelial carcinoma of the bladder treated with radical cystectomy. Ann Surg Oncol. 2022;29(8):5307–5316.t. doi: 10.1245/s10434-022-11575-4

[152] Huang Y, Miao H, Xia C, et al. High VCAM-1 predicts poor prognosis and is associated with chemotherapy resistance in nasopharyngeal carcinoma. Onco Targets Ther. 2021;14:1633–1641. doi: 10.2147/OTT.S292259

[153] Bulska-Będkowska W, Czajka-Francuz P, Jurek-Cisoń S, et al. The predictive role of serum levels of soluble cell adhesion molecules (sCAMs) in the therapy of advanced breast cancer—a single-centre study. Medicina (Kaunas). 2022;58(2):153. doi: 10.3390/medicina58020153

[154] Liu Y, Lyu J, Bell Burdett K, et al. Prognostic and predictive biomarkers in patients with metastatic colorectal cancer receiving regorafenib. Mol Cancer Ther. 2020;19(10):2146–2154. doi: 10.1158/1535-7163.MCT-20-0249

[155] Sackstein R, Schatton T, Barthel SR. T-lymphocyte homing: an underappreciated yet critical hurdle for successful cancer immunotherapy. Lab Invest. 2017;97(6):669–697. doi: 10.1038/labinvest.2017.25

[156] Taverna D, Moher H, Crowley D, et al. Increased primary tumor growth in mice null for β3- or β3/β5-integrins or selectins. Proc Natl Acad Sci USA. 2004;101(3):763–768. doi: 10.1073/pnas.0307289101

[157] Stark FC, Gurnani K, Sad S, et al. Lack of functional selectin ligand interactions compromises long term tumor protection by CD8+ T cells. PLoS One. 2012;7(2):e32211. doi: 10.1371/journal.pone.0032211

[158] Weishaupt C, Steinert M, Brunner G, et al. Activation of human vascular endothelium in melanoma metastases induces ICAM-1 and E-selectin expression and results in increased infiltration with effector lymphocytes. Exp Dermatol. 2019;28(11):1258–1269. doi: 10.1111/exd.14023

[159] Sackstein R. The first step in adoptive cell immunotherapeutics: assuring cell delivery via glycoengineering. Front Immunol. 2019;9:3084. doi: 10.3389/fimmu.2018.03084

[160] Aires DJ, Yoshida M, Richardson SK, et al. T-cell trafficking plays an essential role in tumor immunity. Lab Invest. 2019;99(1):85–92. doi: 10.1038/s41374-018-0124-6

[161] Rosato A, Zambon A, Macino B, et al. Anti-L-selectin monoclonal antibody treatment in mice enhances tumor growth by preventing CTL sensitization in peripheral lymph nodes draining the tumor area. Int J Cancer. 1996;65(6):847–851.

[162] Hanson EM, Clements VK, Sinha P, et al. Myeloid-derived suppressor cells down-regulate L-selectin expression on CD4+ and CD8+ T cells. J Immunol. 2009;183(2):937–944. doi: 10.4049/jimmunol.0804253

[163] Ku A, Muhitch JB, Powers CA, et al. Tumor-induced MDSC act via remote control to inhibit L-selectin-

dependent adaptive immunity in lymph nodes. Elife. 2016;5:e17375. doi: 10.7554/eLife.17375

[164] Xu W, Li S, Li M, et al. Upregulation of CD3ζ and L-selectin in antigen-specific cytotoxic T lymphocytes by eliminating myeloid-derived suppressor cells with doxorubicin to improve killing efficacy of neuroblastoma cells in vitro. J Clin Lab Anal. 2022;36(1): e24158. doi: 10.1002/jcla.24158

[165] Watson A, Durairaj Ruban RP, Ohme J, et al. L-Selectin enhanced T cells improve the efficacy of cancer immunotherapy. Front Immunol. 2019;10:1321. doi: 10.3389/fimmu.2019.01321

[166] Tsui C, Kretschmer L, Rapelius S, et al. MYB orchestrates T cell exhaustion and response to checkpoint inhibition. Nature. 2022;609(7926):354–360. doi: 10.1038/s41586-022-05105-1

[167] Kumari S, Arora M, Singh J, et al. L-Selectin expression is associated with inflammatory microenvironment and favourable prognosis in breast cancer. 3 Biotech. 2021;11 (2):38. doi: 10.1007/s13205-020-02549-y

[168] Li L, Du X, Fan G. Identifying potential biomarkers of prognostic value in colorectal cancer via tumor microenvironment data mining. Front Genet. 2022;12(12):787208. doi: 10.3389/fgene.2021.787208

[169] Rosato A, Mandruzzato S, Bronte V, et al. Role of anti-LFA-1 and anti-ICAM-1 combined MAb treatment in the rejection of tumors induced by Moloney murine sarcoma virus (M-MSV). Intl J Cancer. 1995;61(3):355–362. doi: 10.1002/ijc.2910610314

[170] Cavallo F, Martin-Fontecha A, Bellone M, et al. Co-expression of B7–1 and ICAM-1 on tumors is required for rejection and the establishment of a memory response. Eur J Immunol. 1995;25 (5):1154–1162. doi: 10.1002/eji.1830250504

[171] Fisher DT, Chen Q, Skitzki JJ, et al. IL-6 trans-signaling licenses mouse and human tumor microvascular gateways for trafficking of cytotoxic T cells. J Clin Invest. 2011;121 (10):3846–3859. doi: 10.1172/JCI44952

[172] Regev O, Kizner M, Roncato F, et al. ICAM-1 on breast cancer cells suppresses lung metastasis but is dispensable for tumor growth and killing by cytotoxic T cells. Front Immunol. 2022;13(13):849701. doi: 10.3389/fimmu.2022.849701

[173] Figenschau SL, Knutsen E, Urbarova I, et al. ICAM1 expression is induced by proinflammatory cytokines and associated with TLS formation in aggressive breast cancer subtypes. Sci Rep. 2018;8(1):11720. doi: 10.1038/s41598-018-29604-2

[174] Yamada M, Yanaba K, Hasegawa M, et al. Regulation of local and metastatic host-mediated anti-tumour mechanisms by L-selectin and intercellular adhesion molecule-1. Clin Exp Immunol. 2005;143(2):216–227. doi: 10.1111/j.1365-2249.2005.02989.x

[175] Liu Z, Guo B, Lopez RD. Expression of intercellular adhesion molecule (ICAM)-1 or ICAM-2 is critical in determining sensitivity of pancreatic cancer cells to cytolysis by human γδ-T cells: implications in the design of γδ-T-cell-based immunotherapies for pancreatic cancer. J Of Gastro And Hepatol. 2009;24 (5):900–911. doi: 10.1111/j.1440-1746.2008.05668.x

[176] Yanguas A, Garasa S, Teijeira Á, et al. ICAM-1-LFA-1 dependent CD8+ T-Lymphocyte aggregation in tumor tissue prevents recirculation to draining lymph nodes. Front Immunol. 2018;9(9):2084. doi: 10.3389/fimmu.2018.02084

[177] Yang M, Liu J, Piao C, et al. ICAM-1 suppresses tumor metastasis by inhibiting macrophage M2 polarization through blockade of efferocytosis. Cell Death Dis. 2015;6(6):e1780. doi: 10.1038/cddis.2015.144

[178] Cao W, Chen Y, Han W, et al. Potentiality of α-fetoprotein (AFP) and soluble intercellular adhesion molecule-1 (sICAM-1) in prognosis prediction and immunotherapy response for patients with hepatocellular carcinoma. Bioengineered. 2021;12 (2):9435–9451. doi: 10.1080/21655979.2021.1990195

[179] Taggart D, Andreou T, Scott KJ, et al. Anti–PD-1/anti–CTLA-4 efficacy in melanoma brain metastases depends on extracranial disease and augmentation of CD8 + T cell trafficking. Proc Natl Acad Sci USA. 2018;115(7). doi: 10.1073/pnas.1714089115

[180] Schneider H, Valk E, da Rocha Dias S, et al. CTLA-4 up-regulation of lymphocyte function-associated antigen 1 adhesion and clustering as an alternate basis for coreceptor function. Proc Natl Acad Sci USA. 2005;102 (36):12861–12866. doi: 10.1073/pnas.0505802102

[181] Wu X, Giobbie-Hurder A, Liao X, et al. VEGF neutralization plus CTLA-4 blockade alters soluble and cellular factors associated with enhancing lymphocyte infiltration and humoral recognition in melanoma. Cancer Immunol Res. 2016;4(10):858–868. doi: 10.1158/2326-6066.CIR-16-0084

[182] Yang Y, McCloskey JE, Yang H, et al. Bispecific CAR T cells against EpCAM and inducible ICAM-1 overcome antigen heterogeneity and generate superior antitumor responses. Cancer Immunol Res. 2021;9 (10):1158–1174. doi: 10.1158/2326-6066.CIR-21-0062

[183] Gray KD, McCloskey JE, Vedvyas Y, et al. PD1 blockade enhances ICAM1-directed CAR T therapeutic efficacy in advanced thyroid cancer. Clin Cancer Res. 2020;26 (22):6003–6016. doi: 10.1158/1078-0432.CCR-20-1523

[184] Biele E, Schober SJ, Prexler C, et al. Monocyte maturation mediators upregulate CD83, ICAM-1 and MHC class 1 expression on Ewing's sarcoma, enhancing T cell cytotoxicity. Cells. 2021;10 (11):3070. doi: 10.3390/cells10113070

[185] Tanaka H, Yashiro M, Sunami T, et al. ICAM-2 gene therapy for peritoneal dissemination of scirrhous gastric carcinoma. Clin Cancer Res. 2004;10(14):4885–4892. doi: 10.1158/1078-0432.CCR-0393-03

[186] Perez OD, Kinoshita S, Hitoshi Y, et al. Activation of the PKB/AKT pathway by ICAM-2. Immunity. 2002;16 (1):51–65. doi: 10.1016/S1074-7613(02)00266-2

[187] Nakajima K, Ino Y, Yamazaki-Itoh R, et al. IAP inhibitor, Embelin increases VCAM-1 levels on the endothelium, producing lymphocytic infiltration and antitumor immunity. Oncoimmunol. 2020;9 (1):1838812. doi: 10.1080/2162402X.2020.1838812

[188] Sasaki K, Pardee AD, Qu Y, et al. IL-4 suppresses very late antigen-4 expression which is required for therapeutic Th1 T-cell trafficking into tumors. J Immunother. 2009;32(8):793–802. doi: 10.1097/CJI.0b013e3181acec1e

[189] Sasaki K, Zhao X, Pardee AD, et al. Stat6 signaling suppresses VLA-4 expression by CD8+ T cells and

limits their ability to infiltrate tumor lesions in vivo. J Immunol. 2008;181(1):104–108. doi: 10.4049/jimmunol.181.1.104

[190] Campisi M, Sundararaman SK, Shelton SE, et al. Tumor-derived cGAMP regulates activation of the vasculature. Front Immunol. 2020;11(11):2090. doi: 10.3389/fimmu.2020.02090

[191] Riegler J, Gill H, Ogasawara A, et al. VCAM-1 density and tumor perfusion predict T-cell infiltration and treatment response in preclinical models. Neoplasia. 2019;21(10):1036–1050. doi: 10.1016/j.neo.2019.08.003

[192] Carbone F, Ministrini S, Bonaventura A, et al. Serum levels of VCAM-1 are associated with survival in patients treated with nivolumab for NSCLC. Eur J Clin Investigation. 2022;52(1):e13668. doi: 10.1111/eci.13668

[193] Bose A, Taylor JL, Alber S, et al. Sunitinib facilitates the activation and recruitment of therapeutic anti-tumor immunity in concert with specific vaccination. Int J Cancer. 2011;129(9):2158–2170. doi: 10.1002/ijc.25863

[194] Garbi N, Arnold B, Gordon S, et al. CpG motifs as proinflammatory factors render autochthonous tumors permissive for infiltration and destruction. J Immunol. 2004;172(10):5861–5869. doi: 10.4049/jimmunol.172.10.5861

[195] Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. Nature. 2011 May 19;473(7347):298–307. doi: 10.1038/nature10144

[196] Baluk P, Hashizume H, McDonald DM. Cellular abnormalities of blood vessels as targets in cancer. Curr Opin Genet Dev. 2005;15(1):102–111. doi: 10.1016/j.gde.2004.12.005

[197] Bouzin C, Brouet A, De Vriese J, et al. Effects of vascular endothelial growth factor on the lymphocyte-endothelium interactions: identification of caveolin-1 and nitric oxide as control points of endothelial cell anergy. J Immunol. 2007 Feb 1;178(3):1505–1511. doi: 10.4049/jimmunol.178.3.1505

[198] Huang H, Langenkamp E, Georganaki M, et al. VEGF suppresses T-lymphocyte infiltration in the tumor microenvironment through inhibition of nf-κB-induced endothelial activation. Faseb J. 2015;29(1):227–238. doi: 10.1096/fj.14-250985

[199] Griffioen A, Damen CA, Blijham GH, et al. Tumor angiogenesis is accompanied by a decreased inflammatory response of tumor-associated endothelium. Blood. 1996 Jul 15;88(2):667–673. doi: 10.1182/blood.V88.2.667.bloodjournal882667