

REVIEW

ICAM-1: A master regulator of cellular responses in inflammation, injury resolution, and tumorigenesis

Triet M. Bui | Hannah L. Wiesolek | Ronen Sumagin 

Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Correspondence

Ronen Sumagin, Department of Pathology, Feinberg School of Medicine, Northwestern University, Tarry Building 3-707, 300 East Superior Street, Chicago, IL 60611, USA.
E-mail: ronen.sumagin@northwestern.edu

Abstract

ICAM-1 is a cell surface glycoprotein and an adhesion receptor that is best known for regulating leukocyte recruitment from circulation to sites of inflammation. However, in addition to vascular endothelial cells, ICAM-1 expression is also robustly induced on epithelial and immune cells in response to inflammatory stimulation. Importantly, ICAM-1 serves as a biosensor to transduce outside-in-signaling via association of its cytoplasmic domain with the actin cytoskeleton following ligand engagement of the extracellular domain. Thus, ICAM-1 has emerged as a master regulator of many essential cellular functions both at the onset and at the resolution of pathologic conditions. Because the role of ICAM-1 in driving inflammatory responses is well recognized, this review will mainly focus on newly emerging roles of ICAM-1 in epithelial injury-resolution responses, as well as immune cell effector function in inflammation and tumorigenesis. ICAM-1 has been of clinical and therapeutic interest for some time now; however, several attempts at inhibiting its function to improve injury resolution have failed. Perhaps, better understanding of its beneficial roles in resolution of inflammation or its emerging function in tumorigenesis will spark new interest in revisiting the clinical value of ICAM-1 as a potential therapeutic target.

KEYWORDS

adhesion molecules, immune cells, Inflammation, metastasis, migration, tumorigenesis, wound healing

1 | INTRODUCTION

Adhesion molecules are critical regulators of cellular function, tissue integrity, and homeostasis. These adhesive receptors not only mediate cell-to-cell interactions, but through association with the cell cytoskeleton and various adaptor proteins trigger intracellular signaling events in response to specific and local cues.^{1,2} As such, adhesion molecules help form endothelial and epithelial barriers via signal transduction and homotypic interactions at cellular junctions,

while providing structural support and binding scaffold for extracellular matrix (ECM), glycocalyx, and many resident or recruited cell types via heterotypic interactions at the basal and apical membranes.²

ICAM-1 is a cell surface glycoprotein expressed at a low basal level in immune, endothelial (EC) and epithelial cells, but is up-regulated in response to inflammatory stimulation.³ The function of ICAM-1 has been best studied in leukocyte transendothelial migration (TEM), where ICAM-1 regulates leukocyte rolling and adhesive interactions with the vessel wall, and guides leukocyte crossing of the endothelial layer.^{4,5} More recently, functional studies identified several new roles of ICAM-1 in epithelial injury-resolution responses, innate and adaptive immune responses in inflammation, and tumorigenesis.⁶

Thus, ICAM-1 has emerged as a master regulator of many essential tissue functions both at the onset and the resolution of pathologic conditions. ICAM-1 has been of clinical and therapeutic interest for some time now; however, inhibition of ICAM-1 function has not yielded significant clinical impact in improving injury resolution.⁷⁻⁹ Perhaps, with a better understanding of its various roles in health

Abbreviations: COPD, Chronic obstructive pulmonary disease; CTCs, Circulating tumor cells; DCs, Dendritic cells; EAE, Experimental autoimmune encephalomyelitis; ECM, Extracellular matrix; ECs, Endothelial cells; EPCs, Endothelial progenitor cells; ERM, Ezrin, radixin, and moesin; IBD, Inflammatory bowel disease; IECs, Intestinal epithelial cells; LFA-1, Lymphocyte function-associated antigen 1; Mac-1, Macrophage antigen 1; MIP-2, Macrophage inflammatory protein 2; MLCK, Myosin light-chain kinase; MUC1, Mucin 1; NSCLC, Nonsmall cell lung carcinoma; PKC, Protein kinase C; PMNs, Polymorphonuclear neutrophils; Rac, Ras-related C3 botulinum toxin substrate; ROS, Reactive oxygen species; SCLC, Small cell lung carcinoma; sICAM-1, soluble ICAM-1; TEM, Transendothelial migration; TLS, Tertiary lymphoid structures; TME, Tumor microenvironment; TNBC, Triple-negative breast cancer.

and disease and new mechanistic insights into its function, the clinical value of ICAM-1 could be revisited for improvement of therapeutic strategies. This review will summarize the emerging aspects of ICAM-1 biology, its diverse functions in disease, and the potential diagnostic and therapeutic implications associated with this adhesion receptor.

2 | ICAM-1 STRUCTURE AND FUNCTIONAL IMPLICATIONS DURING HOMEOSTASIS AND PATHOGENESIS

2.1 | ICAM-1 structure, splice variants, and glycosylation

ICAM-1 belongs to the Ig superfamily and consists of five extracellular Ig domains, a transmembrane domain, and a short cytoplasmic domain.¹⁰ The molecular weight of ICAM-1 varies between 60 and 114 kDa, depending on the extent of glycosylation on the Ig domains.¹¹ These glycosylated Ig domains mediate ICAM-1 interactions with its ligands. Upon ligation, ICAM-1 undergoes dimerization and clustering through homotypic binding between Ig domains 3 and 4,¹² which significantly increases ICAM-1 binding affinity to its cognate ligands β_2 -integrins lymphocyte function-associated antigen 1 (LFA-1; CD11a/CD18) and macrophage antigen 1 (Mac-1; CD11b/CD18).^{13,14} LFA-1 and Mac-1 are known to bind Ig domains 1 and 3, respectively.¹⁵

As with other Ig superfamily members, ICAM-1 is post-transcriptionally regulated by alternative splicing, which generates six membrane-bound variants and a secretable soluble protein (sICAM-1).^{16,17} Structural studies of ICAM-1 reported that all ICAM-1 isoforms consist of at least Ig domains 1 and 5, and the variable domains 2, 3, and 4, which define ICAM-1 binding specificity to its ligands.¹⁶ Thus, alternative splicing can dictate ICAM-1 function in various pathologic conditions.¹⁸ Supporting this idea, disrupting different Ig domains of ICAM-1 to generate knockout (KO) mouse models can differentially impact disease outcomes. For example, *Icam1*^{tm1Jcgr} mice with truncated Ig domain 3 showed impaired neutrophil (polymorphonuclear neutrophils [PMN]) recruitment and exhibited resistance to endotoxic shock.^{18,19} In contrast, *Icam1*^{tm1Bay} mice lacking isoforms with Ig domain 4 were highly susceptible to endotoxemia with undisturbed or even enhanced neutrophil infiltration.^{18,20}

Intriguingly in experimental autoimmune encephalomyelitis (EAE), whereas ICAM-1 is up-regulated by EC and many other cell types, disease symptoms were reduced in ICAM-1 null mice (*Icam1*^{tm1Alb}) but were unexpectedly exacerbated in *Icam1*^{tm1Bay}, possibly due to T-cell dysfunction.^{18,21,22} As with endotoxemia, *Icam1*^{tm1Jcgr} were resistant to EAE with less immune cell infiltration.^{18,21,23} The findings underscore the potentially distinct roles of ICAM-1 splice variants in immune disorders.

Glycosylation is another factor that can significantly affect ICAM-1 function.²⁴ ICAM-1 is heavily glycosylated, and variations in glycosylation were shown to result in distinct biologic functions.²⁵ It has been shown that N-glycans on the Ig domains of ICAM-1 are required for retention of the receptor on the cell surface.^{24,26} In the context of

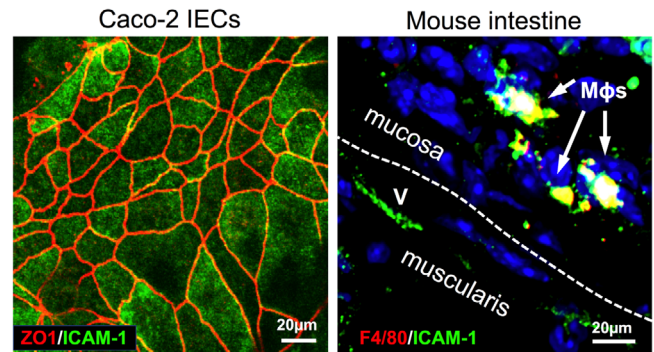


FIGURE 1 ICAM-1 expression on endothelial, epithelial, and immune cells. Representative immunofluorescence images show ICAM-1 expression on the surface of intestinal epithelial cells, Caco2 (left, co-stained with the junctional molecule ZO-1), and on macrophages and endothelial cells in inflamed mouse colon tissue (right). Colon inflammation was induced by dextran sodium sulfate (DSS) treatment (3% weight/volume). Following 4 d of treatment colon tissue was extracted, sectioned, and stained using standard protocols. ICAM-1 expressing, F4/80 positive tissue Mφs shown by white arrows, (v) depicts blood vessels, the white dashed line separates the muscularis and mucosa layers. Scale bars represent 20 μ m

leukocyte trafficking, high-mannose form of ICAM-1 was found to be more efficient at regulating monocyte rolling and adhesion, whereas the complex N-glycan form of ICAM-1 was required for cytoskeletal changes in ECs and thus in the regulation of vascular permeability.²⁷ Furthermore, changes in protein glycosylation can alter cleavage by proteinases, thus impacting the release and the structure of sICAM-1.²⁸ This will in turn impact ICAM-1 function, as will be discussed in following sections.

3 | ICAM-1 EXPRESSION AND FUNCTION IN INFLAMMATION

ICAM-1 is expressed at low levels by EC, epithelial, and immune cells. ICAM-1 expression is highly induced by a variety of inflammatory cytokines; however, a degree of specificity among different cell types has been observed.^{3,29} For example, in ECs, ICAM-1 expression was induced by NF- κ B in response to TNF α or IL-1 β stimulation,³⁰ whereas in intestinal epithelial cells (IECs), ICAM-1 expression was induced by IFN γ , but not by TNF α or LPS treatment.³¹ In macrophages, IFN γ and LPS stimulation induced a robust up-regulation of ICAM-1 compared to relatively small effect of TNF α or IL-1 β .³² ICAM-1 expression was also shown to be regulated by microRNA activity. MiR-141 in ECs was found to down-regulate ICAM-1, thus decreasing leukocyte adhesion and attenuating myocardial ischemia-reperfusion injury.³³ Because ICAM-1 is induced in many cell types during inflammatory responses, it is not surprising that ICAM-1 has been implicated in many physiologic processes, including leukocyte trafficking, immune cell effector functions, pathogen and dead cell clearance, and T-cell activation. Figure 1 demonstrates the expression of ICAM-1 on epithelial, EC, and immune cells in response to inflammation.

3.1 | ICAM-1 regulates leukocyte trafficking and effector function

ICAM-1 is best known for its role in regulating leukocyte trafficking and TEM.^{34,35} The role of ICAM-1 in leukocyte-EC interactions has been well studied and elegantly summarized in several recent reviews³⁶⁻³⁸ and will not be discussed in detail. However, it is worth noting that in addition to its well-established role in mediating leukocyte firm adhesion to ECs, ICAM-1 has been shown to also mediate slow PMN rolling and luminal crawling.³⁹⁻⁴¹

Intriguingly, in post-capillary venules, whereas expression of ICAM-1 was increased with inflammatory stimulus, high and low ICAM-1 expression regions along the vessel wall were observed.⁴² Not surprisingly, leukocyte interactions in these respective regions were increased or decreased accordingly.⁴⁰ Moreover, ICAM-1 expression patterns varied among individual ECs and were also shown to actively redistribute and cluster around migrating leukocytes.^{43,44} ICAM-1 enrichment at the tricellular EC junction was also noted, marking these regions as preferred locations or “portals” of entry for PMN TEM.⁴⁵

ICAM-1 contributions to immune cell effector function are also being increasingly recognized. For example, ICAM-1 expressed by dendritic or natural killer cells is important for T lymphocyte binding and formation of immune synapses.⁴⁶⁻⁴⁸ ICAM-1 expressed by T lymphocytes can deliver a co-stimulatory signal, which is required for T-cell activation,^{49,50} as well as contribute to programming of memory CD8 T cells in response to secondary stimuli.⁵¹ We recently demonstrated that ICAM-1 expression was highly induced in inflammatory macrophages, where it served as a phagocytic receptor and mediated binding of macrophages and apoptotic cells, facilitating apoptotic clearance.³² Finally, ICAM-1 expression was also induced on activated murine and human PMNs. In murine PMNs, LPS-driven induction of ICAM-1 expression was associated with enhanced reactive oxygen species (ROS) generation and improved phagocytoses.^{52,53} Consistently, ICAM-1 expression was also detected on PMNs from patients with bacterial peritonitis and in septic patients with elevated levels of endotoxin.^{53,54} ICAM-1 expression significantly improved PMN effector function in both murine models and human disease.

3.2 | ICAM-1 regulates endothelial and epithelial barrier function

In addition to mediating leukocyte adhesion, ICAM-1 also serves as a signaling receptor to transduce outside-in signaling, linking leukocyte adhesive interactions with epithelial and endothelial function.^{37,55} Specifically, ICAM-1 signals through the association of its cytoplasmic domain with the actin cytoskeleton. These interactions are facilitated via adaptor proteins, including ezrin, radixin, and moesin (ERM),⁵⁶ actinin,⁵⁷ b-tubulin,⁵⁸ glyceraldehyde-3-phosphate dehydrogenase,⁵⁹ cortactin,⁶⁰ Grb2,⁶¹ SOS, and Shc.⁶² ICAM-1 ligation by leukocytes or by crosslinking Abs, which effectively simulates leukocyte binding, has elucidated many signaling events that are induced downstream

of ICAM-1. These include activation of Rho-GTPases,⁶¹ Src kinase and endothelial nitric synthase,⁶³ MAP kinases,⁶⁴ and protein kinase C (PKC).⁶⁵ By signaling through these effector molecules, ICAM-1 contributes to the regulation of critical barrier properties in ECs and epithelial cells. The various signaling pathways regulated by ICAM-1 are summarized in Table 1.

In ECs, ICAM-1 has been shown to regulate intracellular Ca²⁺ levels and lead to activation of myosin contractility, both of which are critical for maintaining a functional barrier.⁶⁶⁻⁶⁸ Moreover, ICAM-1 has been shown to regulate EC permeability in healthy and inflamed tissue.^{44,69,70} Intriguingly, whereas in healthy tissue, ICAM-1 signaled through PKC activation to control barrier function, following inflammatory stimulation, ICAM-1 engagement by circulating leukocytes led to Src kinase activation to increase solute permeability.⁴⁴ ICAM-1 was also shown to activate JNK and lead to internalization of VE-cadherin,⁷⁰ causing disruption of the EC junction and impairment of EC barrier function.⁶⁴ ICAM-1 could also modulate EC permeability by regulating cytokine production. ICAM-1 antibody-crosslink in HUVECs increased production of IL-8 and CCL5,^{64,71,72} where both molecules have been shown to impair EC permeability.⁷³⁻⁷⁵

ICAM-1 is similarly up-regulated in epithelial cells under inflammatory conditions where it primarily localizes to the apical surface.^{31,76-78} In gut epithelium, ICAM-1 expression has been shown to be markedly increased in active inflammatory bowel disease (IBD) and in epithelial cells following inflammatory stimulation.^{31,79} Given its apical (luminal) localization, ICAM-1 has no direct role in mediating PMN migration across IECs as it does in endothelium; however, ICAM-1 promotes retention of transmigrated PMNs at the luminal epithelial surface.³¹ PMN ligation of ICAM-1 at the apical epithelial surface also triggered myosin light-chain kinase (MLCK)-dependent down-regulation of perijunctional F-actin, which increased intestinal epithelial permeability.³¹ In bronchial epithelial cells, ICAM-1 activation by clustering induced local activation of ERK1/2 to modulate permeability.⁸⁰

ICAM-1 can further impact IEC permeability by facilitating ligation of other apically localized proteins by retained PMNs. One such protein is CD44, which similarly to ICAM-1, can associate with ERM proteins to regulate the actin cytoskeleton.^{81,82} In addition, CD44 via recruitment of metalloproteinases (MMP7 and 9) impairs junction assembly and thus compromises epithelial barrier function.⁸³

3.3 | Soluble ICAM-1 as an inflammatory biomarker

ICAM-1 can be also found as an sICAM-1 in numerous inflammatory disorders.⁸⁴⁻⁸⁷ sICAM-1 is produced as a spliced isoform or as a result of proteolytic cleavage.^{18,88} The splice variant of sICAM-1 is truncated at the transmembrane domain whereas it retains all five extracellular Ig domains similarly to full-length ICAM-1 molecule. In contrast, enzymatically cleaved forms of sICAM-1 may differ in the composition of their Ig domains depending on proteases that catalyzed the cleavage. It has been suggested that common proteases including elastase, cathepsins, and metalloproteases can mediate cleavage of ICAM-1, generating potentially structurally different forms of the

TABLE 1 ICAM-1 signaling and function: a summary of ICAM-1 expression, signaling, and regulation of various cellular processes in health and disease as has been discussed in this review

Cell type	Function	Interactions/ signaling	Mechanism of action	Disease model	Refs.
Endothelial cells	Leukocyte adhesion	Adhesive binding	Recruitment and retention of immune cells, Initiation of inflammatory responses	Experimental autoimmune encephalomyelitis (EAE), colitis, Endotoxemia	19-23, 42, 154
	Cell migration	Src kinase, PKC δ	Reorganization of the actin cytoskeleton and cell shape, VEGF production and new vessel formation	Acute lung injury, ischemic injury, sterile inflammation	46, 65, 144, 67
	Barrier function	Ca ²⁺ signaling	Myosin contractility, vascular permeability and immune cell trafficking	Brain injury/sterile inflammation	69, 70, 68
	Proliferation	Nitric synthase	Proliferation; new vessel formation	Lung inflammation	69, 103
	EC activation	MAPK-ERK1/2	Reorganization of the actin cytoskeleton	Kidney injury	152
Epithelial cells	Cell migration	Rac/Rho/Cdc42	Reorganization of the actin cytoskeleton and cell shape, Cell migration, Oncogenic transformation	Lung inflammation	153
	Barrier function	JNK/p38, MLCK	Dissolution of adherens junctions, Loss of the apical F-actin, Cytoskeletal rearrangement	Lung injury, inflammatory bowel disease (IBD)	71, 73, 31, 80
	Proliferation	Akt/ β -catenin	Cell cycle progression and cell growth	Colon injury	115
PMNs	ROS release	<i>Not defined</i>	PMN phagocytosis and cytotoxicity	Peritonitis	52-54
Macrophages	Efferocytosis	Adhesive binding	Phenotypic polarization, macrophage binding to apoptotic/necrotic cells	Intestinal injury	113, 132, 32
T cells	T-cell activation	PI3K	Co-stimulatory receptor for T-cell activation	Inflammation, cell cultures	49-51
Dendritic cells	T-cell activation	<i>Not defined</i>	Chemokines release for T-cell activation	Inflammation, cell cultures	47-48
Cancer cells	Cellular adhesion	Adhesive binding	TLS formation and increase tumor immunogenicity, CTCs retention at the vessel walls at metastatic sites	Breast cancer, melanoma, liver metastasis	133, 139-141, 143, 144, 174-178
	Cell migration	MAPK-ERK1/2 (?)	Reorganization of cytoskeleton, cancer cell invasion		
	Transformation	Src kinase (?)	Oncogenic transformation		

protein.^{17,18} However, whether this also results in different biologic functions of sICAM-1 during inflammation is not yet determined.

sICAM-1 levels are elevated in animal disease models⁸⁹⁻⁹¹ and in serum of patients with chronic obstructive pulmonary disease (COPD),⁹² asthma,⁹³ sepsis,⁹⁴ atherosclerosis,⁹⁵ coronary heart disease,⁹⁶ or cancer.⁹⁷⁻⁹⁹ Increases in sICAM levels were correlated with inflammation and several clinical studies used sICAM-1 as a

surrogate marker to monitor response to therapy (particularly in clinical studies of cancer patients, will be discussed in the following text) or for classifying patients with infectious versus noninfectious systemic inflammatory response syndrome,⁸⁷ as well as a variety of inflammatory disorders.⁸⁹⁻⁹¹

sICAM-1 has been shown to promote both pro- and anti-inflammatory responses. Low levels of sICAM-1 have been shown

to trigger activation of NF κ B and ERK, leading to the release of inflammatory cytokines macrophage inflammatory protein (MIP)-1a, MIP-2, TNF α , IFN γ , and IL-6 (summarized in³⁷). In contrast, high levels of sICAM-1 enhanced EC migration and angiogenesis,^{100,101} competitively inhibited leukocyte-EC interactions,¹⁰² and promoted the pro-repair activity of immune cells.¹⁰³ Several emerging roles of sICAM-1 in resolution of inflammation will be discussed in the following section.

4 | ICAM-1 CONTRIBUTES TO RESOLUTION OF INFLAMMATION AND WOUND HEALING

Restoration of tissue homeostasis following pathogenic insult or injury initiates with inflammatory resolution, which involves clearance of inflammatory immune cells and reprogramming of tissue resident cells to pro-resolution phenotype.^{104,105} The subsequent tissue remodeling phase involves re-epithelialization (restitution and regeneration of injured tissue), vascularization, and formation of new capillary networks.¹⁰⁶ ICAM-1 function is typically associated with progressing inflammation; however, emerging evidence increasingly implicates ICAM-1 activity in resolution of inflammation and wound healing.

4.1 | ICAM-1 and immune cell effector function in resolution of inflammation

Macrophages are professional phagocytes in charge of wound debridement and clearance of apoptotic/dead cells by efferocytosis.^{107,108} As such, macrophages play an important role in timely resolution of inflammation and successful wound healing.^{109,110} We found that ICAM-1 expressed by inflammatory macrophages played an important role in efferocytosis (clearance of apoptotic/dead cells) of immune and epithelial cells.³² Efferocytosis also leads to cellular reprogramming in newly recruited inflammatory macrophages, which in turn suppress inflammatory response and increase production of pro-resolution cytokines, including IL-10, TGF- β , and PGE2.^{111,112} Furthermore, ICAM-1 was found to directly impact macrophage polarization and promote the pro-repair phenotype by positively modulating miR-124 expression.¹¹³ Thus, by enhancing macrophage efferocytosis and the pro-repair reprogramming, ICAM-1 can contribute to inflammatory resolution and tissue healing. ICAM-1 expressed by T cells was found to function as a co-stimulatory molecule to promote T-cell activation,⁵⁰ where activated regulatory T cells promote the pro-repair function of macrophage by increasing efferocytosis and production of IL-10.¹¹⁴ Finally, ICAM-1 improved PMN effector function (ROS generation and phagocytoses) in murine endotoxemia model and septic patients to facilitate inflammatory resolution.⁵²⁻⁵⁴

4.2 | ICAM-1 in epithelial and endothelial wound healing

ICAM-1 in epithelial cells has been implicated in regulating wound healing.¹¹⁵⁻¹¹⁷ In IECs, engagement of ICAM-1 by apically adherent

PMNs induced Akt phosphorylation and Akt-dependent transcriptional activation of β -catenin, leading to increased IEC proliferation and wound re-epithelialization.¹¹⁵ Whereas colon wound healing was impaired in ICAM-1 KO mice, an induction of epithelial ICAM-1 signaling at the wound bed by ICAM-1-targeted immune complexes significantly improved colon wound healing, supporting the role of ICAM-1 in this process.¹¹⁵ Similarly, ICAM-1 has been shown to promote skin wound healing, where the loss of ICAM-1 has been linked to impaired keratinocyte migration, granulation tissue formation, and overall inhibition of wound healing. However, in this setting, impaired wound repair was associated with ICAM-1-dependent reduction in infiltrating neutrophils and macrophages.¹¹⁶ ICAM-1 in corneal epithelium has been shown to promote corneal wound repair by facilitating the recruitment and retention of γ/δ T cells, which are important mediators of resolution of inflammation and wound healing. With the loss of corneal epithelial ICAM-1, T-cell recruitment was impaired, as was epithelial cell division and subsequent re-epithelialization.¹¹⁸

Finally, ICAM-1 has also been implicated in EC migration and repair,¹⁰¹ which is critical for neovascularization of resealing wounds and restoration of tissue homeostasis.^{109,110} ICAM-1 has been shown to regulate EC migration by activating Akt and endothelial nitric synthase.¹⁰¹ Besides, EC ICAM-1 has been also shown to mediate recruitment of bone marrow-derived endothelial progenitor cells (EPCs) in ischemic hearts to promote angiogenesis following injury.¹¹⁹ Similarly, sICAM-1 has been shown to stimulate EC migration and tube formation.¹⁰⁰ Because de novo production or generation of sICAM-1 by cleavage is elevated in inflammation,^{17,120-122} sICAM-1 may facilitate resolution of inflammation and enhance wound healing by promoting neovascularization.

5 | ICAM-1 ACTIVITY IMPACTS TUMOR DEVELOPMENT AND METASTASIS

Cellular constituents of tumor microenvironment (TME) include tumor and stromal cells, blood and lymph vessels, as well as infiltrating and resident immune cells.^{123,124} Expression of ICAM-1 has been documented in most, if not all, cell types in the TME.^{125,126} As such, in lung adenocarcinoma, ICAM-1 was shown to be induced in transformed alveolar epithelial cells, ECs, pulmonary lymphocytes, and fibroblast.¹²⁷⁻¹²⁹ In melanoma, thin pre-cancerous lesions expressed a negligible amount of ICAM-1; however, analyses of multilayered melanoma lesions revealed heightened ICAM-1 expression at the basal layer.^{130,131} ICAM-1 expression has been similarly induced in tumor-associated macrophages, and was involved in their polarization.^{113,132} As with the primary tumor site, ICAM-1 up-regulation was also documented during metastasis.^{133,134} Studies in experimental liver metastasis model revealed elevated ICAM-1 levels on liver sinusoid ECs, hepatocytes, Kupffer cells, and interstitial fibroblasts.^{125,135} An induction of ICAM-1 expression by tumor resident and infiltrating cells both at the primary and secondary sites indicates an important role of this receptor during tumorigenesis.

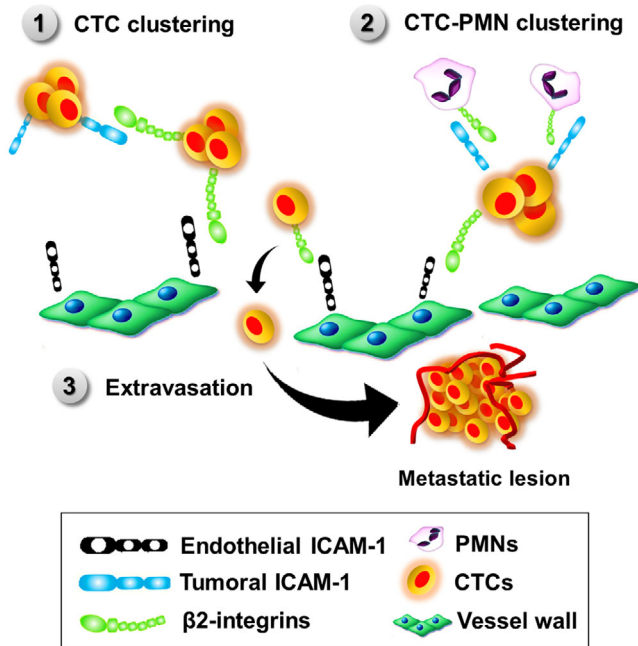


FIGURE 2 Potential mechanisms of action by which ICAM-1 may promote tumor metastasis. (1) Via binding to β_2 -integrins expressing tumor cells, ICAM-1 may support homotypic clustering of circulating tumor cells (CTCs). CTC clusters showed increased survival and metastatic potential. (2) Via β_2 -integrins expressed by immune cells, ICAM-1 can promote CTC-leukocyte clustering β_2 -integrin. Association of CTC clusters with polymorphonuclear neutrophils increased survival and proliferation of tumor cells. (3) ICAM-1 expressed by endothelial cells can facilitate capture and extravasation of β_2 -integrin-expressing tumor hijacking transendothelial migration mechanisms used by migrating leukocytes

5.1 | ICAM-1 confers aggressive phenotype to cancer cells of the primary tumor niche

ICAM-1 expression has been correlated with aggressive and invasive tumor phenotypes. For example, transcriptional profiling of several triple-negative breast cancer (TNBC) cell lines identified ICAM-1 as one of the top differentially expressed genes compared to other breast cancer cells.¹³⁶ ICAM-1 was constitutively expressed in basal-like, TNBC cancer cells (most aggressive breast cancer subtype associated with poor prognosis) whereas only inducible in human epidermal growth factor receptor 2 and luminal B cancer subtypes, and was completely absent in luminal A (less aggressive) subtype of breast cancer. As with breast cancer, ICAM-1 expression is significantly induced in nonsmall cell lung carcinoma (NSCLC), which is an aggressive and highly metastatic type of lung cancer, whereas was found to be constitutively expressed at relatively low levels by small cell lung carcinoma (SCLC) cells.^{137,138}

Given its putative properties, ICAM-1 expressed by tumor cells can impact tumor development either by promoting tumor-immune cell adhesive interactions or by relaying outside-in signaling to regulate tumor cell function. Supporting the idea of ICAM-1-dependent retention of immune cells, histologic analyses of breast cancer tissue correlated high ICAM-1 expression in TNBC with the presence of tertiary

lymphoid structures (TLS).¹³⁹ These T-cell-rich regions are closely associated with invasive and highly immunogenic tumors. Similarly, ICAM-1 expressed by tumor and stromal cells in a melanoma xenograft model was found to promote T-cell aggregation and retention at the tumor niche through binding to β_2 -integrin LFA-1.¹⁴⁰ Although T-cell recruitment and retention due to ICAM-1 on one hand may improve the immunosurveillance and potentially restrict tumor development, T-cell aggregation within the tumor tissues has been shown to impair the effector function of infiltrating T cells, allowing tumor cells to evade immune recognition and killing.

Interestingly, analyses of tumor sections from patients with TNBC revealed that ICAM-1-expressing tumor cells were localized to tumor invasive front, a region that was also heavily infiltrated by immune cells, particularly T lymphocytes.^{136,139} Similarly, in squamous cell oral carcinoma ICAM-1 was enriched at the invading basal layer, where accumulating T cells were observed and where immunogenic responses were driven by T-cell-dependent IFN- γ signaling.¹⁴¹ This suggests that tumor infiltrating immune cells via cytokine release may drive expression of ICAM-1 in tumor cells, and as such promote tumor-immune cell interactions and enhance directional cancer cell migration. Indeed, IFN- γ has been shown to induce ICAM-1 expression in cancer cells,¹⁴² and in turn, ICAM-1 has been implicated in promoting cancer cell migration.^{143,144}

Although specific ICAM-1 signaling in tumor cells that may enhance migration has not been well defined, evidence from other biologic systems indicates several potential signaling pathways. For example, ICAM-1 through binding interactions with mucin 1 (MUC1), which is overexpressed in breast, ovarian, prostate, and gastric cancers, can activate the pro-migratory MAPK/ERK signaling cascade in neighboring tumor cells.¹⁴⁵⁻¹⁴⁸ ICAM-1 can also interact with the ECM components such as fibrinogen to stimulate pro-migratory signaling.^{149,150} In ECs, engagement of ICAM-1 by immune cells triggered intracellular Ca^{2+} increases⁶⁶ and activation of Src kinase⁶³ and Ras-related C3 botulinum toxin substrate (Rac)/Cdc42 GTPases,¹⁵¹⁻¹⁵³ all of which can promote cell migration. ICAM-1 may similarly act in transformed epithelial and tumor cells to promote migratory and invasive phenotypes, yet this remains to be determined.

Finally, ICAM-1 up-regulation was also noted in hypoxic tissue,¹⁵⁴ where HIF-1 and NF- κ B signaling axes are substantially activated. Interestingly, in HUVEC cultured under severe hypoxic condition, the induction of ICAM-1 expression was regulated in prolyl hydroxylase (PHD) and NF- κ B-dependent manner, and was independent of HIF-1 signaling.¹⁵⁴ Because oxygen depletion and hypoxia are prominent features of many solid tumors, hypoxic activation of ICAM-1 is likely to govern ICAM-1 signaling and impact tumor viability and transformation.

5.2 | ICAM-1 roles in the initiation and progression of tumor metastasis

Metastasis is a leading cause for cancer-associated mortality.¹⁵⁵ Cancer cells spread to secondary organs by detaching from the primary tumor and subsequently entering the circulation. Circulating

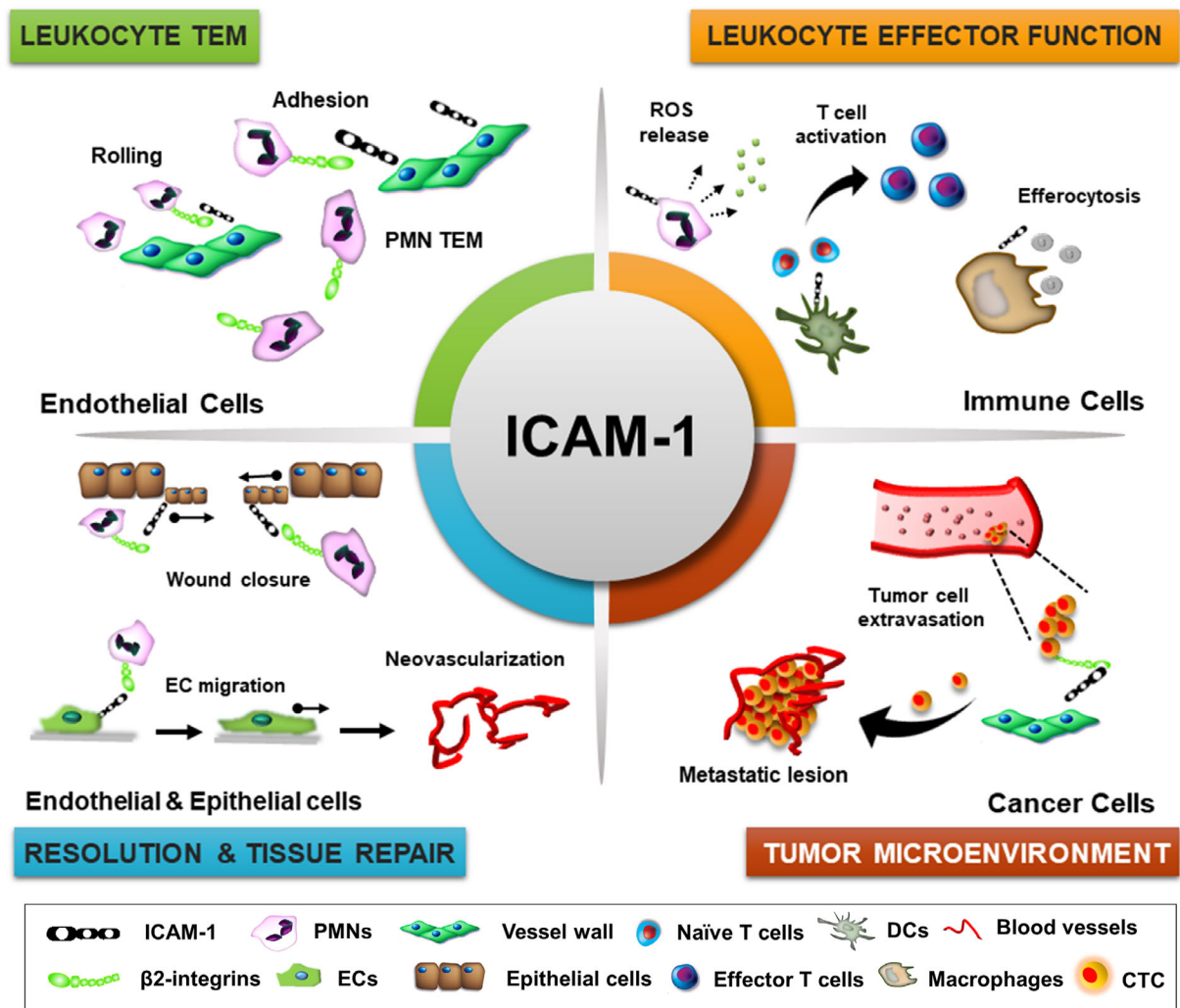


FIGURE 3 ICAM-1 function in tissue homeostasis and disease. Schematic representation of key physiologic processes regulated by ICAM-1. These include leukocyte-endothelial cell interactions and TEM, regulation of leukocyte effector function in inflammation (ROS release by PMNs, T-cell priming and activation by dendritic cells, macrophage efferocytosis and polarization), tissue repair by promoting neovascularization and reepithelialization, and carcinogenesis by facilitating circulating tumor cell extravasation and survival

tumor cells (CTCs) then traverse to distal sites to form metastatic lesions.^{156,157} Although the number of CTCs compared to other blood cells is negligible, recent advances in CTC detection methods established CTCs at the forefront of cancer diagnosis, characterization, and therapeutics.^{158,159} Importantly, the strict correlation between the number of CTCs and increased risk of metastasis and poor patient survival has been demonstrated.¹⁶⁰⁻¹⁶²

Survival of CTCs in the bloodstream and homing to secondary organs is essential for metastases formation.¹⁶³⁻¹⁶⁶ Intriguingly, emerging evidence indicates a potential role of ICAM-1 in the regulation of both processes. Analyses of CTCs from breast cancer patients and mouse xenograft models revealed that in circulation, tumor cells tend to attach to each other, forming CTC clusters.^{164,167,168} Within these clusters, CTCs are protected from the harsh environment in the circulation and display increased proliferative capacity and metastatic potential.¹⁶⁷ However, the mechanisms that drive CTC clustering are not yet defined. This raises intriguing questions of whether these

clusters formed early upon cancer cells leaving the primary tumors, or assembled later in circulation due to hemodynamic factors. CTC clusters were further found to associate with immune cells, particularly with PMNs, and these associations were surprisingly diminished upon CTC cluster disassembly.¹⁶⁷ These exciting observations underscore a potential role of PMNs and likely other circulating immune cells in regulating CTC survival and motility, and as a result, metastatic properties. This of course merits extensive investigation in the future. Because many tumor cell subtypes and immune cells co-express ICAM-1 and various ICAM-1 ligands, including β_2 -integrins, MUC1, and CD44, it is possible that ICAM-1 plays an important role in the heterotypic clustering of CTCs and PMNs observed in these studies. Based on the above discussion, potential mechanisms by which ICAM-1 may facilitate tumor metastasis are illustrated in Fig. 2.

The process of CTC homing to secondary organs is also a topic of continued investigation. CTCs (likely in the case of CTC clusters) may become trapped in the post-capillary venules in the lung, spleen, or

liver,¹⁶⁹ and upon intraluminal proliferation can give rise to secondary tumors.¹⁷⁰⁻¹⁷² CTCs may also hijack mechanisms governing leukocyte recruitment to extravasate from the circulation into the surrounding tissue. In this process, ICAM-1 expressed by ECs will be a key regulatory player. Indeed, inhibition or KO of EC ICAM-1 or CD18 subunit on melanoma, bladder, and breast cancer cells in vitro, significantly attenuated cancer cell adhesion to ECs and subsequent TEM.^{131,173} As a result of ICAM-1 inhibition, tumor cell invasion and metastasis was similarly attenuated in vivo in several metastatic cancer models.¹⁷⁴⁻¹⁷⁸

In addition to capturing CTCs from the circulation, EC ICAM-1 may promote CTC diapedesis by modulating immune cell behavior. ICAM-1 mediates PMN adhesion to ECs, which leads to PMN degranulation¹⁷⁹ and release of various proteinases, including elastase, MMPs, and cathepsins.^{180,181} Disruption of EC junctions by circulating proteinases may create optimal sites for CTC TEM to occur. Additionally, ligation of EC ICAM-1 by interacting PMNs has been shown to induce MLCK-dependent cytoskeletal rearrangement and increase vascular permeability,⁸⁰ creating endothelial barrier conditions advantageous for tumor cell TEM. Consistent with this idea, ICAM-1 is constitutively expressed on the sinusoid microvessels of lung and liver,^{135,182,183} both of which by far represent the most frequent organs of metastasis.

5.3 | ICAM-1 as a prognostic cancer marker

Although it is clear that ICAM-1 expression is highly induced in the TME, the prognostic value of ICAM-1 on clinical outcomes of cancer patient is still somewhat controversial. Most of the evidence (as discussed earlier) suggests the pro-tumorigenic function of ICAM-1. In many cancers, including oral squamous cell carcinoma, lung carcinoma, gastric, and breast cancers, ICAM-1 has been implicated in promoting cancer,^{136,141,184-186} whereas in colorectal and non-Hodgkin's lymphoma, high levels of tumoral ICAM-1 was predictive of favorable clinical outcomes.^{187,188}

In lung NSCLC (high ICAM-1 levels and highly invasive tumors), high serum level of sICAM-1 strongly correlated with poor response to chemotherapy and decreased patient survival, whereas this correlation was insignificant in SCLC.¹⁸⁹⁻¹⁹¹ In addition, a phase III study for the approval of VEGF-A inhibitor bevacizumab (Avastin), where 878 lung cancer patients were randomized into paclitaxel/carboplatin (standard of care) with or without the addition of bevacizumab, has reported a strict correlation between low levels of sICAM-1 and better response to chemotherapy.¹⁹² Specifically, the subgroup with low sICAM-1 had a response rate of 32% to bevacizumab + standard, whereas subgroup with high sICAM-1 had a diminished response rate of 14%. These clinical observations indicate the prognostic value of sICAM-1 in therapeutic response in distinct cancer subtypes.

ICAM-1 levels were also shown to be indicative of tumor grade and as such may have prognostic value in metastatic diseases. A prognostic study comparing 332 patients with benign lung diseases to 387 patients with lung cancer found that patients with advanced tumor stage (stage IV, high metastatic risk) had higher sICAM-1 levels than those with a lower stage.¹⁹³ Specifically within stage IV subgroup,

patients with detectable metastasis had significantly higher sICAM-1 levels compared to those with localized diseases. These observations support ICAM-1 contributions to metastatic progression, as has been observed in pre-clinical studies using animal models.

Finally, there have been efforts to utilize ICAM-1 as a tumor-targeted molecule for therapeutic delivery and diagnostic purpose. As such, ICAM-1 was used to specifically target iron oxide nanoparticles to TNBC, which is currently lacking specific biomarkers and is challenging to diagnose.¹³⁶ The deposition of these iron particles significantly enhanced signals of magnetic resonance imaging, and helped screening of TNBC in a timely and accurate manner. In another setting, ICAM-1 was engineered as a target moiety to deliver doxorubicin-conjugated liposomes to metastatic melanoma and enhanced drug uptake by these cancer cells.¹⁹⁴

6 | CONCLUDING REMARKS

In summary, ICAM-1 serves as an adhesion molecule and as a signaling receptor in many cells types to mount inflammatory responses, initiate resolution of inflammation and healing, and regulate tumor cell survival and dissemination. These concepts are summarized in Fig. 3. As such, although well studied, ICAM-1 remains the focus of continued investigations and may serve as a promising prognostic biomarker, and a potential target for emerging therapies.

AUTHORSHIP

T.M.B., H.L.W., and R.S designed and wrote the manuscript.

ACKNOWLEDGMENTS

We thank the Latin American Association of Immunology (ALAI) and the Mexican Society of Immunology (SMI) for an exciting meeting in Mexico City (2018) and an opportunity to write this review. We also acknowledge support from U.S. National Institutes of Health Grant DK116663, Digestive Health Foundation, American Cancer Society Research Scholar Award, and Crohn's & Colitis Foundation Senior Research Award.

DISCLOSURES

The authors declare no conflicts of interest.

ORCID

Ronen Sumagin  <https://orcid.org/0000-0002-5689-1100>

REFERENCES

1. Harjunpaa H, Lloret Asens M, Guenther C, Fagerholm SC. Cell adhesion molecules and their roles and regulation in the immune and tumor microenvironment. *Front Immunol*. 2019;10:1078.
2. Cavallaro U, Dejana E. Adhesion molecule signalling: not always a sticky business. *Nature Rev Mol Cell Biol*. 2011;12:189-197.

3. Hubbard AK, Rothlein R. Intercellular adhesion molecule-1 (ICAM-1) expression and cell signaling cascades. *Free Radical Biol Med*. 2000;28:1379-1386.
4. Wee H, Oh HM, Jo JH, Jun CD. ICAM-1/LFA-1 interaction contributes to the induction of endothelial cell-cell separation: implication for enhanced leukocyte diapedesis. *Exp Mol Med*. 2009;41:341-348.
5. Gorina R, Lyck R, Vestweber D, Engelhardt B. beta2 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;192:324-337.
6. Kong DH, Kim YK, Kim MR, Jang JH, Lee S. Emerging roles of vascular cell adhesion molecule-1 (VCAM-1) in immunological disorders and cancer. *Int J Mol Sci*. 2018;19.
7. Wichert S, Juliusson G, Johansson A, et al. A single-arm, open-label, phase 2 clinical trial evaluating disease response following treatment with BI-505, a human anti-intercellular adhesion molecule-1 monoclonal antibody, in patients with smoldering multiple myeloma. *PLoS One*. 2017;12:e0171205.
8. Philpott JR. Antisense inhibition of ICAM-1 expression as therapy provides insight into basic inflammatory pathways through early experiences in IBD. *Expert Opin Biol Ther*. 2008;8:1627-1632.
9. Yacyshyn B, Chey WY, Wedel MK, et al. A randomized, double-masked, placebo-controlled study of alicaforsen, an antisense inhibitor of intercellular adhesion molecule 1, for the treatment of subjects with active Crohn's disease. *Clin Gastroenterol Hepatol*. 2007;5:215-220.
10. Staunton DE, Marlin SD, Stratowa C, Dustin ML, Springer TA. Primary structure of ICAM-1 demonstrates interaction between members of the immunoglobulin and integrin supergene families. *Cell*. 1988;52:925-933.
11. Staunton DE, Dustin ML, Erickson HP, Springer TA. The arrangement of the immunoglobulin-like domains of ICAM-1 and the binding sites for LFA-1 and rhinovirus. *Cell*. 1990;61:243-254.
12. Chen X, Kim TD, Carman CV, Mi LZ, Song G, Springer TA. Structural plasticity in Ig superfamily domain 4 of ICAM-1 mediates cell surface dimerization. *PNAS*. 2007;104:15358-15363.
13. Miller J, Knorr R, Ferrone M, Houdei R, Carron CP, Dustin ML. Intercellular adhesion molecule-1 dimerization and its consequences for adhesion mediated by lymphocyte function associated-1. *J Exp Med*. 1995;182:1231-1241.
14. Frick C, Odermatt A, Zen K, et al. Interaction of ICAM-1 with beta 2-integrin CD11c/CD18: characterization of a peptide ligand that mimics a putative binding site on domain D4 of ICAM-1. *Eur J Immunol*. 2005;35:3610-3621.
15. Diamond MS, Staunton DE, Marlin SD, Springer TA. Binding of the integrin Mac-1 (CD11b/CD18) to the third immunoglobulin-like domain of ICAM-1 (CD54) and its regulation by glycosylation. *Cell*. 1991;65:961-971.
16. King PD, Sandberg ET, Selvakumar A, Fang P, Beaudet AL, Dupont B. Novel isoforms of murine intercellular adhesion molecule-1 generated by alternative RNA splicing. *J Immunol*. 1995;154:6080-6093.
17. Robledo O, Papaioannou A, Ochiatti B, et al. ICAM-1 isoforms: specific activity and sensitivity to cleavage by leukocyte elastase and cathepsin G. *Eur J Immunol*. 2003;33:1351-1360.
18. Ramos TN, Bullard DC, Barnum SR. ICAM-1: isoforms and phenotypes. *J Immunol*. 2014;192:4469-4474.
19. Xu H, Gonzalo JA, St Pierre Y, et al. Leukocytosis and resistance to septic shock in intercellular adhesion molecule 1-deficient mice. *J Exp Med*. 1994;180:95-109.
20. Sligh JE, Jr, Ballantyne CM, Rich SS, et al. Inflammatory and immune responses are impaired in mice deficient in intercellular adhesion molecule 1. *PNAS*. 1993;90:8529-8533.
21. Bullard DC, Hu X, Crawford D, McDonald K, Ramos TN, Barnum SR. Expression of a single ICAM-1 isoform on T cells is sufficient for development of experimental autoimmune encephalomyelitis. *Eur J Immunol*. 2014;44:1194-1199.
22. Hu X, Barnum SR, Wohler JE, Schoeb TR, Bullard DC. Differential ICAM-1 isoform expression regulates the development and progression of experimental autoimmune encephalomyelitis. *Mol Immunol*. 2010;47:1692-1700.
23. Samoilova EB, Horton JL, Chen Y. Experimental autoimmune encephalomyelitis in intercellular adhesion molecule-1-deficient mice. *Cell Immunol*. 1998;190:83-89.
24. Scott DW, Patel RP. Endothelial heterogeneity and adhesion molecules N-glycosylation: implications in leukocyte trafficking in inflammation. *Glycobiology*. 2013;23:622-633.
25. Scott DW, Vallejo MO, Patel RP. Heterogenic endothelial responses to inflammation: role for differential N-glycosylation and vascular bed of origin. *J Am Heart Assoc*. 2013;2:e000263.
26. He P, Srikrishna G, Freeze HH. N-glycosylation deficiency reduces ICAM-1 induction and impairs inflammatory response. *Glycobiology*. 2014;24:392-398.
27. Scott DW, Dunn TS, Ballestas ME, Litovsky SH, Patel RP. Identification of a high-mannose ICAM-1 glycoform: effects of ICAM-1 hypoglycosylation on monocyte adhesion and outside in signaling. *Am J Physiol Cell Physiol*. 2013;305:C228-C237.
28. Scott DW, Tolbert CE, Graham DM, Wittchen E, Bear JE, Burridge K. N-glycosylation controls the function of junctional adhesion molecule-A. *Mol Biol Cell*. 2015;26:3205-3214.
29. Roebuck KA, Finnegan A. Regulation of intercellular adhesion molecule-1 (CD54) gene expression. *J Leukoc Biol*. 1999;66:876-888.
30. Sakurada S, Kato T, Okamoto T. Induction of cytokines and ICAM-1 by proinflammatory cytokines in primary rheumatoid synovial fibroblasts and inhibition by N-acetyl-L-cysteine and aspirin. *Int Immunol*. 1996;8:1483-1493.
31. Sumagin R, Robin AZ, Nusrat A, Parkos CA. Transmigrated neutrophils in the intestinal lumen engage ICAM-1 to regulate the epithelial barrier and neutrophil recruitment. *Mucosal Immunol*. 2014;7:905-915.
32. Wiesolek HL, Bui TM, Lee JJ, et al. ICAM-1 functions as an efferocytosis receptor in inflammatory macrophages. *Am J Pathol*. 2020.
33. Liu RR, Li J, Gong JY, et al. MicroRNA-141 regulates the expression level of ICAM-1 on endothelium to decrease myocardial ischemia-reperfusion injury. *Am J Physiol Heart Circ Physiol*. 2015;309:H1303-1313.
34. Oppenheimer-Marks N, Davis LS, Bogue DT, et al. Differential utilization of ICAM-1 and VCAM-1 during the adhesion and transendothelial migration of human T lymphocytes. *J Immunol*. 1991;147:2913-2921.
35. Kanter E, van Rijssel J, Hensbergen PJ, et al. Filamin B mediates ICAM-1-driven leukocyte transendothelial migration. *J Biol Chem*. 2008;283:31830-31839.
36. Lyck R, Enzmann G. The physiological roles of ICAM-1 and ICAM-2 in neutrophil migration into tissues. *Curr Opin Hematol*. 2015;22:53-59.
37. Lawson C, Wolf S. ICAM-1 signaling in endothelial cells. *Pharmacol Rep: PR*. 2009;61:22-32.
38. Rahman A, Fazal F. Hug tightly and say goodbye: role of endothelial ICAM-1 in leukocyte transmigration. *Antioxid Redox Signaling*. 2009;11:823-839.
39. Li N, Yang H, Wang M, Lu S, Zhang Y, Long M. Ligand-specific binding forces of LFA-1 and Mac-1 in neutrophil adhesion and crawling. *Mol Biol Cell*. 2018;29:408-418.
40. Sumagin R, Sarelius IH. A role for ICAM-1 in maintenance of leukocyte-endothelial cell rolling interactions in inflamed arterioles. *Am J Physiol Heart Circ Physiol*. 2007;293:H2786-98.
41. Sumagin R, Prizant H, Lomakina E, Waugh RE, Sarelius IH. LFA-1 and Mac-1 define characteristically different intraluminal crawling and emigration patterns for monocytes and neutrophils in situ. *J Immunol*. 2010;185:7057-7066.

42. Sumagin R, Lamkin-Kennard KA, Sarelius IH. A separate role for ICAM-1 and fluid shear in regulating leukocyte interactions with straight regions of venular wall and venular convergences. *Microcirculation*. 2009;16:508-520.
43. Sumagin R, Sarelius IH. TNF- α activation of arterioles and venules alters distribution and levels of ICAM-1 and affects leukocyte-endothelial cell interactions. *Am J Physiol Heart Circ Physiol*. 2006;291:H2116-25.
44. Sumagin R, Lomakina E, Sarelius IH. Leukocyte-endothelial cell interactions are linked to vascular permeability via ICAM-1-mediated signaling. *Am J Physiol Heart Circ Physiol*. 2008;295:H969-H977.
45. Sumagin R, Sarelius IH. Intercellular adhesion molecule-1 enrichment near tricellular endothelial junctions is preferentially associated with leukocyte transmigration and signals for reorganization of these junctions to accommodate leukocyte passage. *J Immunol*. 2010;184:5242-5252.
46. Bromley SK, Dustin ML. Stimulation of naive T-cell adhesion and immunological synapse formation by chemokine-dependent and -independent mechanisms. *Immunology*. 2002;106:289-298.
47. Goldstein JS, Chen T, Gubina E, Pastor RW, Kozlowski S. ICAM-1 enhances MHC-peptide activation of CD8(+) T cells without an organized immunological synapse. *Eur J Immunol*. 2000;30:3266-3270.
48. Real E, Kaiser A, Raposo G, et al. Immature dendritic cells (DCs) use chemokines and intercellular adhesion molecule (ICAM)-1, but not DC-specific ICAM-3-grabbing nonintegrin, to stimulate CD4+ T cells in the absence of exogenous antigen. *J Immunol*. 2004;173:50-60.
49. Kohlmeier JE, Rumsey LM, Chan MA, Benedict SH. The outcome of T-cell costimulation through intercellular adhesion molecule-1 differs from costimulation through leukocyte function-associated antigen-1. *Immunology*. 2003;108:152-157.
50. Chirathaworn C, Kohlmeier JE, Tibbetts SA, Rumsey LM, Chan MA, Benedict SH. Stimulation through intercellular adhesion molecule-1 provides a second signal for T cell activation. *J Immunol*. 2002;168:5530-5537.
51. Cox MA, Barnum SR, Bullard DC, Zajac AJ. ICAM-1-dependent tuning of memory CD8 T-cell responses following acute infection. *PNAS*. 2013;110:1416-1421.
52. Elsner J, Sach M, Knopf HP, et al. Synthesis and surface expression of ICAM-1 in polymorphonuclear neutrophilic leukocytes in normal subjects and during inflammatory disease. *Immunobiology*. 1995;193:456-464.
53. Woodfin A, Beyrau M, Voisin MB, et al. ICAM-1-expressing neutrophils exhibit enhanced effector functions in murine models of endotoxemia. *Blood*. 2016;127:898-907.
54. Wang SZ, Smith PK, Lovejoy M, Bowden JJ, Alpers JH, Forsyth KD. Shedding of L-selectin and PECAM-1 and upregulation of Mac-1 and ICAM-1 on neutrophils in RSV bronchiolitis. *Am J Physiol*. 1998;275:L983-9.
55. Lefort CT, Hyun YM, Schultz JB, et al. Outside-in signal transmission by conformational changes in integrin Mac-1. *J Immunol*. 2009;183:6460-6468.
56. Barreiro O, Yanez-Mo M, Serrador JM, et al. Dynamic interaction of VCAM-1 and ICAM-1 with moesin and ezrin in a novel endothelial docking structure for adherent leukocytes. *J Cell Biol*. 2002;157:1233-1245.
57. Carpen O, Pallai P, Staunton DE, Springer TA. Association of intercellular adhesion molecule-1 (ICAM-1) with actin-containing cytoskeleton and alpha-actinin. *J Cell Biol*. 1992;118:1223-1234.
58. Couty JP, Rampon C, Leveque M, et al. PECAM-1 engagement counteracts ICAM-1-induced signaling in brain vascular endothelial cells. *J Neurochem*. 2007;103:793-801.
59. Federici C, Camoin L, Hattab M, Strosberg AD, Couraud PO. Association of the cytoplasmic domain of intercellular-adhesion molecule-1 with glyceraldehyde-3-phosphate dehydrogenase and beta-tubulin. *FEBS*. 1996;238:173-180.
60. Yang L, Kowalski JR, Yacono P, et al. Endothelial cell cortactin coordinates intercellular adhesion molecule-1 clustering and actin cytoskeleton remodeling during polymorphonuclear leukocyte adhesion and transmigration. *J Immunol*. 2006;177:6440-6449.
61. Etienne S, Adamson P, Greenwood J, Strosberg AD, Cazaubon S, Couraud PO. ICAM-1 signaling pathways associated with Rho activation in microvascular brain endothelial cells. *J Immunol*. 1998;161:5755-5761.
62. Gardiner EE, D'Souza SE. Sequences within fibrinogen and intercellular adhesion molecule-1 (ICAM-1) modulate signals required for mitogenesis. *J Biol Chem*. 1999;274:11930-11936.
63. Liu G, Place AT, Chen Z, et al. ICAM-1-activated Src and eNOS signaling increase endothelial cell surface PECAM-1 adhesivity and neutrophil transmigration. *Blood*. 2012;120:1942-1952.
64. Dragoni S, Hudson N, Kenny BA, et al. Endothelial MAPKs direct ICAM-1 signaling to divergent inflammatory functions. *J Immunol*. 2017;198:4074-4085.
65. Rahman A, Anwar KN, Uddin S, et al. Protein kinase C-delta regulates thrombin-induced ICAM-1 gene expression in endothelial cells via activation of p38 mitogen-activated protein kinase. *Mol Cell Biol*. 2001;21:5554-5565.
66. Etienne-Manneville S, Manneville JB, Adamson P, Wilbourn B, Greenwood J, Couraud PO. ICAM-1-coupled cytoskeletal rearrangements and transendothelial lymphocyte migration involve intracellular calcium signaling in brain endothelial cell lines. *J Immunol*. 2000;165:3375-3383.
67. Renkonen R, Mennander A, Ustinov J, Mattila P. Activation of protein kinase C is crucial in the regulation of ICAM-1 expression on endothelial cells by interferon-gamma. *Int Immunol*. 1990;2:719-724.
68. Bonan S, Albregues J, Grasset E, et al. Membrane-bound ICAM-1 contributes to the onset of proinvasive tumor stroma by controlling actin-myosin contractility in carcinoma-associated fibroblasts. *Oncotarget*. 2017;8:1304-1320.
69. Frank PG, Lisanti MP. ICAM-1: role in inflammation and in the regulation of vascular permeability. *Am J Physiol Heart Circ Physiol*. 2008;295:H926-H927.
70. Sarelius IH, Glading AJ. Control of vascular permeability by adhesion molecules. *Tissue Barriers*. 2015;3:e985954.
71. Lawson C, Ainsworth M, Yacoub M, Rose M. Ligation of ICAM-1 on endothelial cells leads to expression of VCAM-1 via a nuclear factor-kappaB-independent mechanism. *J Immunol*. 1999;162:2990-2996.
72. Lomakina EB, Waugh RE. Signaling and dynamics of activation of LFA-1 and Mac-1 by immobilized IL-8. *Cell Mol Bioeng*. 2010;3:106-116.
73. Talavera D, Castillo AM, Dominguez MC, Gutierrez AE, Meza I. IL8 release, tight junction and cytoskeleton dynamic reorganization conducive to permeability increase are induced by dengue virus infection of microvascular endothelial monolayers. *J Gen Virol*. 2004;85:1801-1813.
74. Terao S, Yilmaz G, Stokes KY, et al. Blood cell-derived RANTES mediates cerebral microvascular dysfunction, inflammation, and tissue injury after focal ischemia-reperfusion. *Stroke*. 2008;39:2560-2570.
75. Yu H, Huang X, Ma Y, et al. Interleukin-8 regulates endothelial permeability by down-regulation of tight junction but not dependent on integrins induced focal adhesions. *Int J Biol Sci*. 2013;9:966-979.
76. Tosi MF, Stark JM, Smith CW, Hamedani A, Gruenert DC, Infeld MD. Induction of ICAM-1 expression on human airway epithelial cells by inflammatory cytokines: effects on neutrophil-epithelial cell adhesion. *Am J Respir Cell Mol Biol*. 1992;7:214-221.
77. Dippold W, Wittig B, Schwaible W, Mayet W, Meyer zum Buschenfelde KH. Expression of intercellular adhesion molecule 1 (ICAM-1, CD54) in colonic epithelial cells. *Gut*. 1993;34:1593-1597.
78. Chan SC, Shum DK, Tipoe GL, Mak JC, Leung ET, Ip MS. Upregulation of ICAM-1 expression in bronchial epithelial cells by airway secretions in bronchiectasis. *Respir Med*. 2008;102:287-298.

79. Jones SC, Banks RE, Haidar A, et al. Adhesion molecules in inflammatory bowel disease. *Gut*. 1995;36:724-730.
80. Choi H, Fleming NW, Serikov VB. Contact activation via ICAM-1 induces changes in airway epithelial permeability in vitro. *Immunol Invest*. 2007;36:59-72.
81. Yonemura S, Hirao M, Doi Y, et al. Ezrin/radixin/moesin (ERM) proteins bind to a positively charged amino acid cluster in the juxta-membrane cytoplasmic domain of CD44, CD43, and ICAM-2. *J Cell Biol*. 1998;140:885-895.
82. Tsukita S, Oishi K, Sato N, Sagara J, Kawai A, Tsukita S. ERM family members as molecular linkers between the cell surface glycoprotein CD44 and actin-based cytoskeletons. *J Cell Biol*. 1994;126:391-401.
83. Kirschner N, Haftek M, Niessen CM, et al. CD44 regulates tight-junction assembly and barrier function. *J Invest Dermatol*. 2011;131:932-943.
84. Capra F, De Maria E, Lunardi C, et al. Serum level of soluble intercellular adhesion molecule 1 in patients with chronic liver disease related to hepatitis C virus: a prognostic marker for responses to interferon treatment. *J Infect Dis*. 2000;181:425-431.
85. Magro F, Araujo F, Pereira P, Meireles E, Diniz-Ribeiro M, Velosom FT. Soluble selectins, sICAM, sVCAM, and angiogenic proteins in different activity groups of patients with inflammatory bowel disease. *Dig Dis Sci*. 2004;49:1265-1274.
86. Nielsen OH, Brynskov J, Vainer B. Increased mucosal concentrations of soluble intercellular adhesion molecule-1 (sICAM-1), sE-selectin, and interleukin-8 in active ulcerative colitis. *Dig Dis Sci*. 1996;41:1780-1785.
87. de Pablo R, Monserrat J, Reyes E, et al. Circulating sICAM-1 and sE-Selectin as biomarker of infection and prognosis in patients with systemic inflammatory response syndrome. *Eur J Intern Med*. 2013;24:132-138.
88. Wakatsuki T, Kimura K, Kimura F, et al. A distinct mRNA encoding a soluble form of ICAM-1 molecule expressed in human tissues. *Cell Adhes Commun*. 1995;3:283-292.
89. Wang HW, Babic AM, Mitchell HA, Liu K, Wagner DD. Elevated soluble ICAM-1 levels induce immune deficiency and increase adiposity in mice. *FASEB J*. 2005;19:1018-1020.
90. Roescher N, Vosters JL, Yin H, Illei GG, Tak PP, Chiorini JA. Effect of soluble ICAM-1 on a Sjogren's syndrome-like phenotype in NOD mice is disease stage dependent. *PLoS One*. 2011;6:e19962.
91. Laudes IJ, Guo RF, Riedemann NC, et al. Disturbed homeostasis of lung intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 during sepsis. *Am J Pathol*. 2004;164:1435-1445.
92. Lopez-Campos JL, Calero C, Arellano-Orden E, et al. Increased levels of soluble ICAM-1 in chronic obstructive pulmonary disease and resistant smokers are related to active smoking. *Biomark Med*. 2012;6:805-811.
93. Shiota Y, Sato T, Ono T. [Serum levels of soluble ICAM-1 in asthmatic patients]. *Arerugi*. 1993;42:1782-1787.
94. Zonneveld R, Martinelli R, Shapiro NI, et al. Soluble adhesion molecules as markers for sepsis and the potential pathophysiological discrepancy in neonates, children and adults. *Critical Care*. 2014;18:204.
95. Gross MD, Bielinski SJ, Suarez-Lopez JR, et al. Circulating soluble intercellular adhesion molecule 1 and subclinical atherosclerosis: the Coronary Artery Risk Development in Young Adults Study. *Clin Chem*. 2012;58:411-420.
96. Luc G, Arveiler D, Evans A, et al. Circulating soluble adhesion molecules ICAM-1 and VCAM-1 and incident coronary heart disease: the PRIME Study. *Atherosclerosis*. 2003;170:169-176.
97. Kostler WJ, Tomek S, Brodowicz T, et al. Soluble ICAM-1 in breast cancer: clinical significance and biological implications. *Cancer Immunol Immunother*. 2001;50:483-490.
98. Gu X, Ma C, Yuan D, Song Y. Circulating soluble intercellular adhesion molecule-1 in lung cancer: a systematic review. *Transl Lung Cancer Res*. 2012;1:36-44.
99. Giannoulis K, Angouridakis C, Fountzilas G, Papapolychroniadis C, Giannoulis E, Gamvros O. Serum concentrations of soluble ICAM-1 and VCAM-1 in patients with colorectal cancer. Clinical implications. *Tech Coloproctol*. 2004;8(Suppl 1):s65-7.
100. Gho YS, Kleinman HK, Sosne G. Angiogenic activity of human soluble intercellular adhesion molecule-1. *Cancer Res*. 1999;59:5128-5132.
101. Kevil CG, Orr AW, Langston W, et al. Intercellular adhesion molecule-1 (ICAM-1) regulates endothelial cell motility through a nitric oxide-dependent pathway. *J Biol Chem*. 2004;279:19230-19238.
102. Rieckmann P, Michel U, Albrecht M, Bruck W, Wockel L, Felgenhauer K. Soluble forms of intercellular adhesion molecule-1 (ICAM-1) block lymphocyte attachment to cerebral endothelial cells. *J Neuroimmunol*. 1995;60:9-15.
103. Kim JY, Kim DH, Kim JH, et al. Soluble intracellular adhesion molecule-1 secreted by human umbilical cord blood-derived mesenchymal stem cell reduces amyloid-beta plaques. *Cell Death Differ*. 2012;19:680-691.
104. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. *Sci Transl Med*. 2014;6:265sr6.
105. Gonzalez AC, Costa TF, Andrade ZA, Medrado AR. Wound healing - A literature review. *An Bras Dermatol*. 2016;91:614-620.
106. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. *Nature*. 2008;453:314-321.
107. Koh TJ, DiPietro LA. Inflammation and wound healing: the role of the macrophage. *Expert Rev Mol Med*. 2011;13:e23.
108. Mantovani A, Biswas SK, Galdiero MR, Sica A, Locati M. Macrophage plasticity and polarization in tissue repair and remodelling. *J Pathol*. 2013;229:176-185.
109. Tang PM, Nikolic-Paterson DJ, Lan HY. Macrophages: versatile players in renal inflammation and fibrosis. *Nat Rev Nephrol*. 2019;15:144-158.
110. Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. *Immunity*. 2016;44:450-462.
111. Elliott MR, Koster KM, Murphy PS. Efferocytosis signaling in the regulation of macrophage inflammatory responses. *J Immunol*. 2017;198:1387-1394.
112. Korns D, Frasch SC, Fernandez-Boyanapalli R, Henson PM, Bratton DL. Modulation of macrophage efferocytosis in inflammation. *Front Immunol*. 2011;2:57.
113. Gu W, Yao L, Li L, et al. ICAM-1 regulates macrophage polarization by suppressing MCP-1 expression via miR-124 upregulation. *Oncotarget*. 2017;8:111882-111901.
114. Proto JD, Doran AC, Gusarova G, et al. Regulatory T cells promote macrophage efferocytosis during inflammation resolution. *Immunity*. 2018;49:666-677 e6.
115. Sumagin R, Brazil JC, Nava P, et al. Neutrophil interactions with epithelial-expressed ICAM-1 enhances intestinal mucosal wound healing. *Mucosal Immunol*. 2016;9:1151-1162.
116. Nagaoka T, Kaburagi Y, Hamaguchi Y, et al. Delayed wound healing in the absence of intercellular adhesion molecule-1 or L-selectin expression. *Am J Pathol*. 2000;157:237-247.
117. Gay AN, Mushin OP, Lazar DA, et al. Wound healing characteristics of ICAM-1 null mice devoid of all isoforms of ICAM-1. *J Surg Res*. 2011;171:e1-7.
118. Jameson J, Ugarte K, Chen N, et al. A role for skin gammadelta T cells in wound repair. *Science*. 2002;296:747-749.
119. Wu Y, Ip JE, Huang J, et al. Essential role of ICAM-1/CD18 in mediating EPC recruitment, angiogenesis, and repair to the infarcted myocardium. *Circ Res*. 2006;99:315-322.
120. Melotti P, Nicolis E, Tamanini A, Rolfini R, Pavirani A, Cabrini G. Activation of NF-kB mediates ICAM-1 induction in respiratory

- cells exposed to an adenovirus-derived vector. *Gene Ther.* 2001;8:1436-1442.
121. Tong S, Neboori HJ, Tran ED, Schmid-Schonbein GW. Constitutive expression and enzymatic cleavage of ICAM-1 in the spontaneously hypertensive rat. *J Vasc Res.* 2011;48:386-396.
 122. Champagne B, Tremblay P, Cantin A, St Pierre Y. Proteolytic cleavage of ICAM-1 by human neutrophil elastase. *J Immunol.* 1998;161:6398-6405.
 123. Ansell SM, Vonderheide RH. Cellular composition of the tumor microenvironment. *Am Soc Clin Oncol Educ Book.* 2013.
 124. Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. *J Cell Sci.* 2012;125:5591-5596.
 125. Benedicto A, Romayor I, Arteta B. Role of liver ICAM-1 in metastasis. *Oncol Lett.* 2017;14:3883-3892.
 126. Reina M, Espel E. Role of LFA-1 and ICAM-1 in cancer. *Cancers (Basel).* 2017;9(11):153.
 127. Jiang Z, Woda BA, Savas L, Fraire AE. Expression of ICAM-1, VCAM-1, and LFA-1 in adenocarcinoma of the lung with observations on the expression of these adhesion molecules in non-neoplastic lung tissue. *Mod Pathol.* 1998;11:1189-1192.
 128. Passlick B, Izbicki JR, Simmel S, et al. Expression of major histocompatibility class I and class II antigens and intercellular adhesion molecule-1 on operable non-small cell lung carcinomas: frequency and prognostic significance. *Eur J Cancer.* 1994;30A:376-381.
 129. Passlick B, Pantel K, Kubuschok B, et al. Expression of MHC molecules and ICAM-1 on non-small cell lung carcinomas: association with early lymphatic spread of tumour cells. *Eur J Cancer.* 1996;32A:141-145.
 130. Natali P, Nicotra MR, Cavaliere R, et al. Differential expression of intercellular adhesion molecule 1 in primary and metastatic melanoma lesions. *Cancer Res.* 1990;50:1271-1278.
 131. Zhang P, Goodrich C, Fu C, Dong C. Melanoma upregulates ICAM-1 expression on endothelial cells through engagement of tumor CD44 with endothelial E-selectin and activation of a PKC α -p38-SP-1 pathway. *FASEB J.* 2014;28:4591-4609.
 132. Yang M, Liu J, Piao C, Shao J, Du J. ICAM-1 suppresses tumor metastasis by inhibiting macrophage M2 polarization through blockade of efferocytosis. *Cell Death Dis.* 2015;6:e1780.
 133. Rosette C, Roth RB, Oeth P, et al. Role of ICAM1 in invasion of human breast cancer cells. *Carcinogenesis.* 2005;26:943-950.
 134. Sokeland G, Schumacher U. The functional role of integrins during intra- and extravasation within the metastatic cascade. *Mol Cancer.* 2019;18:12.
 135. Benedicto A, Herrero A, Romayor I, et al. Liver sinusoidal endothelial cell ICAM-1 mediated tumor/endothelial crosstalk drives the development of liver metastasis by initiating inflammatory and angiogenic responses. *Sci Rep.* 2019;9:13111.
 136. Guo P, Huang J, Wang L, et al. ICAM-1 as a molecular target for triple negative breast cancer. *PNAS.* 2014;111:14710-14715.
 137. Melis M, Spatafora M, Melodia A, et al. ICAM-1 expression by lung cancer cell lines: effects of upregulation by cytokines on the interaction with LAK cells. *Eur Respir J.* 1996;9:1831-1838.
 138. Schardt C, Heymanns J, Schardt C, Rotsch M, Havemann K. Differential expression of the intercellular adhesion molecule-1 (ICAM-1) in lung cancer cell lines of various histological types. *Eur J Cancer.* 1993;29A:2250-2255.
 139. 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;8:11720.
 140. Yanguas A, Garasa S, Teijeira A, Auba C, Melero I, Rouzaut A. ICAM-1-LFA-1 dependent CD8 $^{+}$ T-lymphocyte aggregation in tumor tissue prevents recirculation to draining lymph nodes. *Front Immunol.* 2018;9:2084.
 141. 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. *Int J Cancer.* 2013;133:568-578.
 142. Chang YJ, Holtzman MJ, Chen CC. Interferon-gamma-induced epithelial ICAM-1 expression and monocyte adhesion. Involvement of protein kinase C-dependent c-Src tyrosine kinase activation pathway. *J Biol Chem.* 2002;277:7118-7126.
 143. Lin YC, Shun CT, Wu MS, Chen CC. A novel anticancer effect of thalidomide: inhibition of intercellular adhesion molecule-1-mediated cell invasion and metastasis through suppression of nuclear factor-kappaB. *Clin Cancer Res.* 2006;12:7165-7173.
 144. Kesanakurti D, Chetty C, Rajasekhar Maddirela D, Gujrati M, Rao JS. Essential role of cooperative NF-kappaB and Stat3 recruitment to ICAM-1 intronic consensus elements in the regulation of radiation-induced invasion and migration in glioma. *Oncogene.* 2013;32:5144-5155.
 145. Hayashi T, Takahashi T, Motoya S, et al. MUC1 mucin core protein binds to the domain 1 of ICAM-1. *Digestion.* 2001;63(Suppl 1):87-92.
 146. Hattrop CL, Gendler SJ. MUC1 alters oncogenic events and transcription in human breast cancer cells. *Breast Cancer Res.* 2006;8:R37.
 147. Yuan Z, Wong S, Borrelli A, Chung MA. Down-regulation of MUC1 in cancer cells inhibits cell migration by promoting E-cadherin/catenin complex formation. *Biochem Biophys Res Commun.* 2007;362:740-746.
 148. Ihermann-Hella A, Lume M, Miinalainen IJ, et al. Mitogen-activated protein kinase (MAPK) pathway regulates branching by remodeling epithelial cell adhesion. *PLoS Genet.* 2014;10:e1004193.
 149. Roche Y, Pasquier D, Rambeaud JJ, Seigneurin D, Duperray A. Fibrinogen mediates bladder cancer cell migration in an ICAM-1-dependent pathway. *Thromb Haemost.* 2003;89:1089-1097.
 150. Tsakadze NL, Zhao Z, D'Souza SE. Interactions of intercellular adhesion molecule-1 with fibrinogen. *Trends Cardiovasc Med.* 2002;12:101-108.
 151. Nurmi SM, Autero M, Raunio AK, Gahmberg CG, Fagerholm SC. Phosphorylation of the LFA-1 integrin beta2-chain on Thr-758 leads to adhesion, Rac-1/Cdc42 activation, and stimulation of CD69 expression in human T cells. *J Biol Chem.* 2007;282:968-975.
 152. Li CH, Liao PL, Shyu MK, et al. Zinc oxide nanoparticles-induced intercellular adhesion molecule 1 expression requires Rac1/Cdc42, mixed lineage kinase 3, and c-Jun N-terminal kinase activation in endothelial cells. *Toxicol Sci.* 2012;126:162-172.
 153. Kim H, Hwang JS, Woo CH, et al. TNF-alpha-induced up-regulation of intercellular adhesion molecule-1 is regulated by a Rac-ROS-dependent cascade in human airway epithelial cells. *Exp Mol Med.* 2008;40:167-175.
 154. Winning S, Splettstoesser F, Fandrey J, Frede S. Acute hypoxia induces HIF-independent monocyte adhesion to endothelial cells through increased intercellular adhesion molecule-1 expression: the role of hypoxic inhibition of prolyl hydroxylase activity for the induction of NF-kappa B. *J Immunol.* 2010;185:1786-1793.
 155. Guan X. Cancer metastases: challenges and opportunities. *Acta Pharm Sin B.* 2015;5:402-418.
 156. Seyfried TN, Huysentruyt LC. On the origin of cancer metastasis. *Crit Rev Oncog.* 2013;18:43-73.
 157. Pantel K, Brakenhoff RH. Dissecting the metastatic cascade. *Nature Rev Cancer.* 2004;4:448-456.
 158. Keller L, Pantel K. Unravelling tumour heterogeneity by single-cell profiling of circulating tumour cells. *Nature Rev Cancer.* 2019;19:553-567.
 159. Tellez-Gabriel M, Brown HK, Young R, Heymann MF, Heymann D. The challenges of detecting circulating tumor cells in sarcoma. *Front Oncol.* 2016;6:202.
 160. Micalizzi DS, Maheswaran S, Haber DA. A conduit to metastasis: circulating tumor cell biology. *Genes Dev.* 2017;31:1827-1840.

161. Shishido SN, Carlsson A, Nieva J, et al. Circulating tumor cells as a response monitor in stage IV non-small cell lung cancer. *J Transl Med*. 2019;17:294.
162. Wang X, Ma K, Yang Z, et al. Systematic correlation analyses of circulating tumor cells with clinical variables and tumor markers in lung cancer patients. *J Cancer*. 2017;8:3099-3104.
163. Kim YR, Yoo JK, Jeong CW, Choi JW. Selective killing of circulating tumor cells prevents metastasis and extends survival. *J Hematol Oncol*. 2018;11:114.
164. Gkoutela S, Castro-Giner F, Szczerba BM, et al. Circulating tumor cell clustering shapes DNA methylation to enable metastasis seeding. *Cell*. 2019;176:98-112 e14.
165. Wang WC, Zhang XF, Peng J, et al. Survival mechanisms and influence factors of circulating tumor cells. *Biomed Res Int*. 2018;2018:6304701.
166. Strlic B, Offermanns S. Intravascular survival and extravasation of tumor cells. *Cancer Cell*. 2017;32:282-293.
167. Szczerba BM, Castro-Giner F, Vetter M, et al. Neutrophils escort circulating tumour cells to enable cell cycle progression. *Nature*. 2019;566:553-557.
168. Saini M, Szczerba BM, Aceto N. Circulating tumor cell-neutrophil tango along the metastatic process. *Cancer Res*. 2019;79:6067-6073.
169. Labelle M, Hynes RO. The initial hours of metastasis: the importance of cooperative host-tumor cell interactions during hematogenous dissemination. *Cancer Discov*. 2012;2:1091-1099.
170. Mekata E, Shimizu T, Endo Y, Tani T. The rapid growth of intraluminal tumor metastases at the intestinal wall sites damaged by obstructive colitis due to sigmoid colon cancer: report of a case. *Surg Today*. 2008;38:862-865.
171. Bhatti N, Gilson RJ, Beecham M, et al. Failure to deliver hepatitis B vaccine: confessions from a genitourinary medicine clinic. *BMJ*. 1991;303:97-101.
172. Takayoshi K, Ariyama H, Tamura S, et al. Intraluminal superior vena cava metastasis from adenosquamous carcinoma of the duodenum: a case report. *Oncol Lett*. 2016;11:605-609.
173. Ghislin S, Obino D, Middendorp S, Boggetto N, Alcaide-Loridan C, Deshayes F. 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;12:455.
174. 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;35:1541-1548.
175. Hamai 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;68:9854-9864.
176. Miele ME, Bennett CF, Miller BE, Welch DR. Enhanced metastatic ability of TNF-alpha-treated malignant melanoma cells is reduced by intercellular adhesion molecule-1 (ICAM-1, CD54) antisense oligonucleotides. *Exp Cell Res*. 1994;214:231-241.
177. Zhu DZ, Cheng CF, Pauli BU. Mediation of lung metastasis of murine melanomas by a lung-specific endothelial cell adhesion molecule. *PNAS*. 1991;88:9568-9572.
178. Zhu D, Cheng CF, Pauli BU. Blocking of lung endothelial cell adhesion molecule-1 (Lu-ECAM-1) inhibits murine melanoma lung metastasis. *J Clin Invest*. 1992;89:1718-1724.
179. Schleiffenbaum B, Moser R, Patarroyo M, Fehr J. The cell surface glycoprotein Mac-1 (CD11b/CD18) mediates neutrophil adhesion and modulates degranulation independently of its quantitative cell surface expression. *J Immunol*. 1989;142:3537-3545.
180. Fedorova NV, Ksenofontov AL, Serebryakova MV, et al. Neutrophils release metalloproteinases during adhesion in the presence of insulin, but cathepsin G in the presence of glucagon. *Mediators Inflamm*. 2018;2018:1574928.
181. Wang S, Dangerfield JP, Young RE, Nourshargh S. PECAM-1, alpha6 integrins and neutrophil elastase cooperate in mediating neutrophil transmigration. *J Cell Sci*. 2005;118:2067-2076.
182. Fingar VH, Taber SW, Buschemeyer WC, et al. Constitutive and stimulated expression of ICAM-1 protein on pulmonary endothelial cells in vivo. *Microvasc Res*. 1997;54:135-144.
183. Nario RC, Hubbard AK. Localization of intercellular adhesion molecule-1 (ICAM-1) in the lungs of silica-exposed mice. *Environ Health Perspect*. 1997;105(Suppl 5):1183-1190.
184. De Vita F, Infusino S, Auriemma A, Orditura M, Catalano G. Circulating levels of soluble intercellular adhesion molecule-1 in non-small cell lung cancer patients. *Oncol Rep*. 1998;5:393-396.
185. Schroder C, Witzel I, Muller V, et al. Prognostic value of intercellular adhesion molecule (ICAM)-1 expression in breast cancer. *J Cancer Res Clin Oncol*. 2011;137:1193-1201.
186. Jung WC, Jang YJ, Kim JH, et al. Expression of intercellular adhesion molecule-1 and e-selectin in gastric cancer and their clinical significance. *J Gastric Cancer*. 2012;12:140-148.
187. Maeda K, Kang SM, Sawada T, et al. Expression of intercellular adhesion molecule-1 and prognosis in colorectal cancer. *Oncol Rep*. 2002;9:511-514.
188. Terol MJ, Lopez-Guillermo A, Bosch F, et al. Expression of the adhesion molecule ICAM-1 in non-Hodgkin's lymphoma: relationship with tumor dissemination and prognostic importance. *J Clin Oncol*. 1998;16:35-40.
189. Shin HS, Jung CH, Park HD, Lee SS. The relationship between the serum intercellular adhesion molecule-1 level and the prognosis of the disease in lung cancer. *Korean J Intern Med*. 2004;19:48-52.
190. Young RJ, Tin AW, Brown NJ, Jitlal M, Lee SM, Woll PJ. Analysis of circulating angiogenic biomarkers from patients in two phase III trials in lung cancer of chemotherapy alone or chemotherapy and thalidomide. *Br J Cancer*. 2012;106:1153-1159.
191. Qian Q, Zhan P, Yu L, et al. Baseline levels and decrease in serum soluble intercellular adhesion molecule-1 during chemotherapy predict objective response and survival in patients who have advanced non-small-cell lung cancer. *Clin Lung Cancer*. 2011;12:131-137.
192. Dowlati A, Gray R, Sandler AB, Schiller JH, Johnson DH. 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;14:1407-1412.
193. Sprenger A, Schardt C, Rotsch M, et al. Soluble intercellular adhesion molecule-1 in patients with lung cancer and benign lung diseases. *J Cancer Res Clin Oncol*. 1997;123:632-638.
194. Guo P, Yang J, Bielenberg DR, et al. A quantitative method for screening and identifying molecular targets for nanomedicine. *J Control Release*. 2017;263:57-67.

How to cite this article: Bui TM, Wiesolek HL, Sumagin R. ICAM-1: A master regulator of cellular responses in inflammation, injury resolution, and tumorigenesis. *J Leukoc Biol*. 2020;1-13. <https://doi.org/10.1002/JLB.2MR0220-549R>