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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

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

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

AUTHORSHIP

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cellular junctions, while providing structural support and binding scaffold for extracellular matrix (ECM), glycocalix, 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 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 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 NFκB in response to TNFα or IL-1β stimulation,[30] whereas in intestinal epithelial cells (IECs), ICAM-1 expression was induced by IFNγ, but not by TNFα or LPS treatment.[31] In macrophages, IFNγ and LPS stimulation induced a robust up-regulation of ICAM-1 compared to relatively small effect of TNFα or IL-1β.[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 reviews[36–38] 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)δ.[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 Ca^{2+} 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 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 models[89–91] 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 NFκB and ERK, leading to the release of inflammatory cytokines macrophage inflammatory protein (MIP)-1a, MIP-2, TNFα, IFNγ, and IL-6 (summarized in[37]). 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-epithelization (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 reprograming, 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 negligent 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.

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+} increases[66] and activation of Src kinase[63] 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 pheno-types, yet this remains to be determined.

Finally, ICAM-1 up-regulation was also noted in hypoxic tissue,[154] where HIF-1 and NFκB 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 NFκB-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 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 negligent, 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 attached 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 degranulation[179] 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 rearrangment 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.

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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

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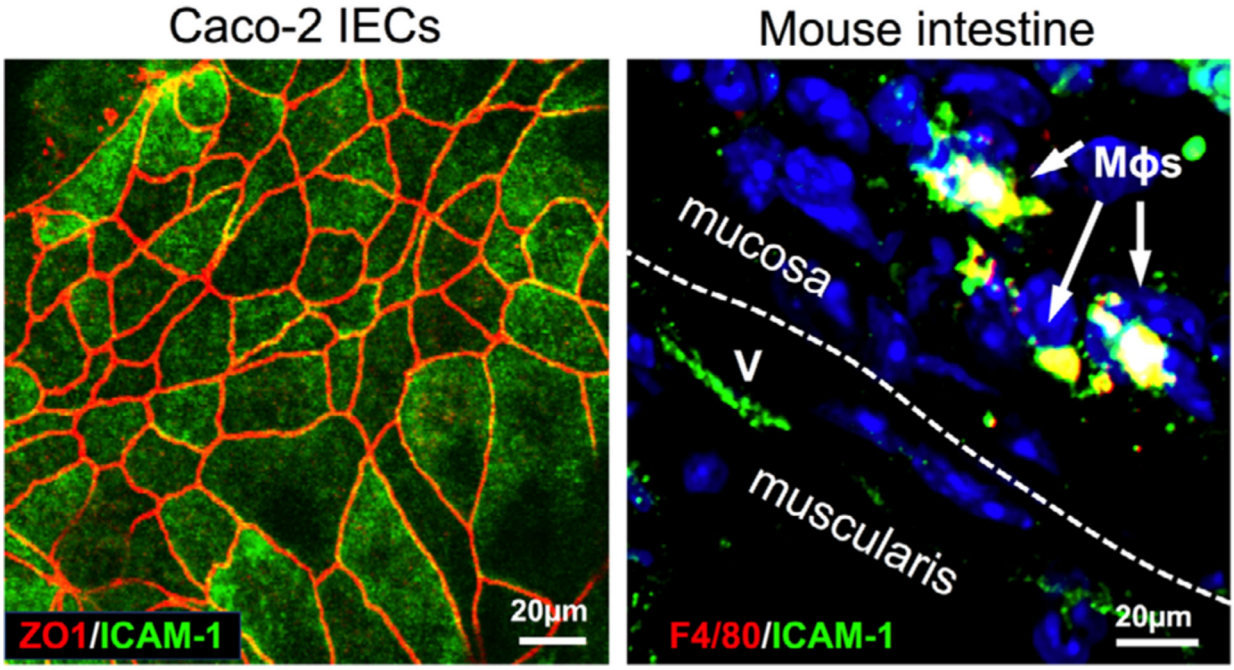

FIGURE 1. ICAM-1 expression on endothelial, epithelial, and immune cells.

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 20μm

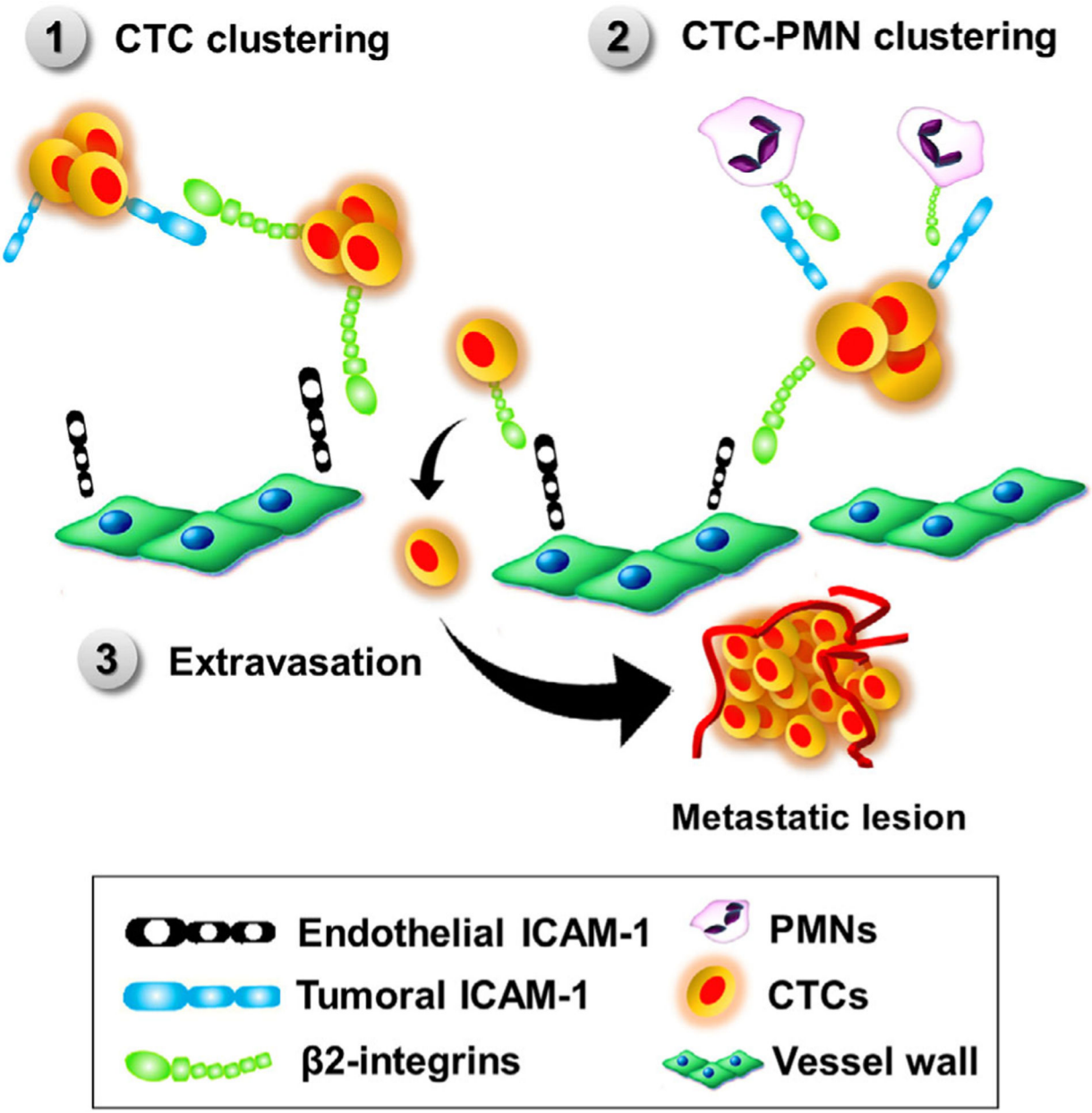

FIGURE 2. Potential mechanisms of action by which ICAM-1 may promote tumor metastasis.
(1) Via binding to β_2-integrins expressing tumor cells, ICAM-1 may support homotypic clustering of circulating tumor cells (CTCs). CTC clusters showed increased survival and metastatic potential. (2) Via β_2-integrins 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

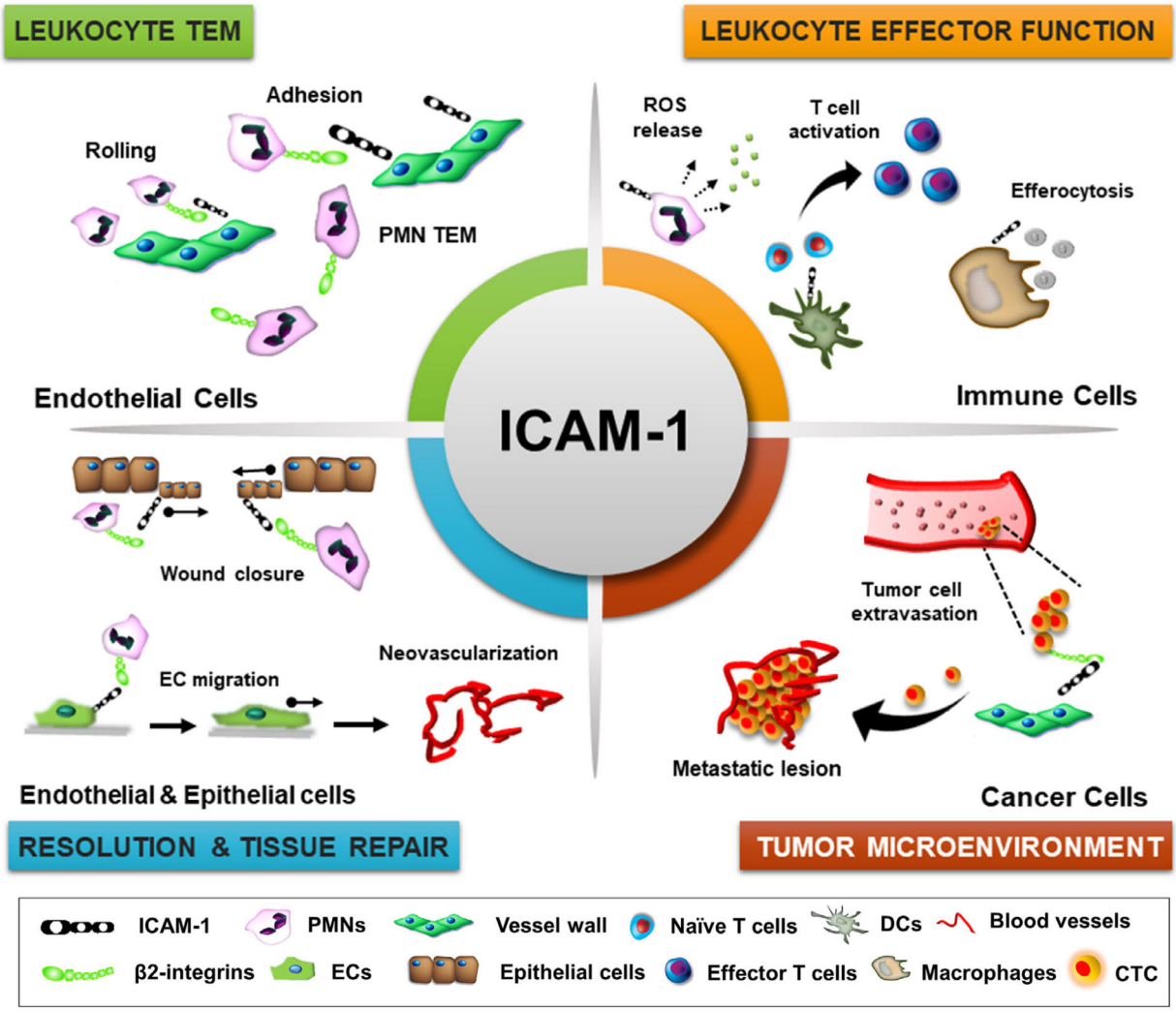

FIGURE 3. ICAM-1 function in tissue homeostasis and disease.

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

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, PKCδ	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	Not defined	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	*Not defined*	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		