J Mol Med (1996) 74:13–33
© Springer-Verlag 1996

REVIEW

A. van de Stolpe · P.T. van der Saag

Intercellular adhesion molecule-1

Received: 20 June 1995 / Accepted: 16 October 1995

Abstract The intercellular adhesion molecule (ICAM) 1 is an Ig-like cell adhesion molecule expressed by several cell types, including leukocytes and endothelial cells. It can be induced in a cell-specific manner by several cytokines, for example, tumor necrosis factor-α, interleukin-1, and interferon-γ, and inhibited by glucocorticoids. Its ligands are the membrane-bound integrin receptors LFA-1 and Mac-1 on leukocytes, CD43, the soluble molecule fibrinogen, the matrix factor hyaluronan, rhinoviruses, and *Plasmodium falciparum* malaria-infected erythrocytes. ICAM-1 expression is predominantly transcriptionally regulated. The ICAM-1 promoter contains several enhancer elements, among them a novel κB element which mediates effects of 12-*O*-tetradecanoylphorbol-13-acetate, interleukin-1, lipopolysaccharide, tumor necrosis factor-α, and glucocorticoids. Expression regulation is cell specific and depends on the availability of cytokine/hormone receptors, signal transduction pathways, transcription factors, and posttranscriptional modification. ICAM-1 plays a role in inflammatory processes and in the T-cell mediated host defense system. It functions as a costimulatory molecule on antigen-presenting cells to activate MHC class II restricted T-cells, and on other cell types in association with MHC class I to activate cytotoxic T-cells. ICAM-1 on endothelium plays an important role in migration of (activated) leukocytes to sites of inflammation. ICAM-1 is shed by the cell and detected in plasma as sICAM-1. Regulation and significance of sICAM-1 are as yet unclear, but sICAM-1 is increased in many pathological conditions. ICAM-1 may play a pathogenetic role in rhinovirus infections. Derangement of ICAM-1 expression probably contributes to the clinical manifestations of a variety of diseases, predominantly by interfering with normal immune function. Among these are malignancies (e.g., melanoma and lymphomas), many inflammatory disorders (e.g., asthma and autoimmune disorders), atherosclerosis, ischemia, certain neurological disorders, and allogeneic organ transplantation. Interference with ICAM-1 leukocyte interaction using mAbs, soluble ICAM-1, antisense ICAM-1 RNA, and in the case of melanoma mAb-coupled immunotoxin, may offer therapeutic possibilities in the future. Integration of knowledge concerning membrane-bound and soluble ICAM-1 into a single functional system is likely to contribute to elucidating the immunoregulatory function of ICAM-1 and its pathophysiological significance in various disease entities.

Key words Adhesion · Intercellular adhesion molecule-1 · Inflammation · Malignancy

Abbreviations *ICAM* Intercellular adhesion molecule · *IFN* Interferon · *IL* Interleukin · *LFA* Leukocyte function associated antigen · *mAb* Monoclonal antibody · *mICAM-1* Membrane-bound ICAM-1 · *NF* Nuclear factor · *NHL* Non-Hodgkin lymphoma · *RAR* Retinoic acid receptor · *sICAM-1* Soluble ICAM-1 · *TNF* Tumor necrosis factor · *TPA* 12-*O*-Tetradecanoylphorbol-13-acetate

Introduction

Adhesion molecules allow cells to adhere to other cells or to extracellular matrix molecules [1–4]. Adhesion processes are required for cells to interact and to migrate to their place of destination. They play a role in many biological processes, as diverse as embryonal development (cellular interaction and migration), immunology (migration and activation of leukocytes), and hematopoiesis (differentiation of hematopoietic cells). With respect to a function in immunology, three important groups of cell adhesion molecules have been described [3].

– *Immunoglobulinlike cell adhesion molecules* (ICAMs), among which ICAM-1 (CD54), ICAM-2 [5], and ICAM-

A. van de Stolpe (✉)
Department of Hematology, University Hospital Nijmegen, Postbus 9101, 6500 HB Nijmegen, The Netherlands

P.T. van der Saag
Hubrecht Laboratory, Netherlands Institute of Developmental Biology, Utrecht, The Netherlands

3 (CD50) [6–8], neural cell adhesion molecule (NCAM) [9], vascular cell adhesion molecule (VCAM) [10], and platelet/endothelial cell adhesion molecule (PECAM) [11]. ICAM-R [8] is identical to ICAM-3. ICAM-1, -2, and -3 are closely related and bind the same integrin receptor, i.e. leukocyte function associated antigen (LFA) 1 [12].

– *Integrins* consist of an α and a β chain. Several subfamilies exist, each characterized by a different β chain [13]. These mediate cell-cell and cell-matrix interactions and transduce signals into the cell. The avidity for their ligands can be regulated. Among the integrins are two receptors for ICAM-1, i.e. LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18), which belong to the β_2 subfamily [3].

– *Selectins* (P, E, and L selectin) are expressed by leukocytes and endothelial cells. These mediate relatively loose contacts between leukocytes and endothelial cells, resulting in "rolling" of leukocytes over the endothelium (see "Function").

The diversity of cell adhesion molecules and the individual regulation of their expression and affinity for the respective ligands indicate that they act in intricate interplay to perform the above functions. This review focuses on ICAM-1, which is indispensable for normal functioning of the immune system [14–20]. Consequently derangement of ICAM-1 expression has been shown to be associated with a variety of disorders, and modulation of ICAM-1 expression or accessability may provide a potential new target for therapeutic intervention in these diseases.

Structure and ligand binding

Structure

ICAM-1 is a transmembrane glycoprotein which belongs to the Ig supergene family and contains five Ig-like domains, similar to ICAM-3 [6, 7], while ICAM-2 has only two Ig-like domains [5]. The murine [21], rat [22], and canine [23] counterparts of human ICAM-1 have also been cloned and cDNA sequences show limited homology to the human sequence (55–65%). The human ICAM-1 gene consists of seven exons separated by six introns. Each of the five Ig-like domains is encoded by a separate exon [24]. The ICAM-1 protein consists of 505 amino acids. The Ig-like domains are formed by 453 predominantly hydrophobic amino acids, followed by a hydrophobic transmembrane domain (24 residues) and a charged cytoplasmic tail (28 residues) [25]. ICAM-1 is differentially glycosylated depending on cell type, giving rise to a molecular weight between 80 and 114 kDa [14, 15, 25]. Deglycosylation of ICAM-1 results in a protein of 60 kDa [14]. The Ig-like domains probably have a β sheet structure, which is stabilized by disulfide bridges between highly conserved cysteine residues in the B and F β strands of the first, second, third, and fifth domains [23, 26]. An exception is the fourth domain where the cysteine in the F β strand is replaced by the hydrophobic amino acid leucine, which has been suggested to stabilize the β sheet [25]. In addition, two cysteines in the flanking E and G β strands of this domain [25] may substitute for the missing cysteine residue in the F β strand. The extracellular region of ICAM-1 forms a hinged rod with a length of approximately 19 nm and width of 2–3 nm, suggesting an end-to-end alignment of Ig domains [26, 27] (Fig. 1). Unlike the usual ligands for receptors of the integrin family, ICAM-1 does not contain a calcium-binding RGD (Arg-Gly-Asp) sequence, suggesting that its conformation is not dependent on the presence of calcium [26, 28]. The presence of free cysteine residues located close to the membrane [25] may allow formation of intermolecular disulfide bonds, suggesting the possibility that ICAM-1 also exists as a dimer.

Connection with the cytoskeleton

ICAM-1 can be distributed in the membrane in a polarized fashion [16, 29–31] and has been shown to associate and colocalize with the cytoskeleton-binding protein α-actinin [29]. Amino acids in the cytoplasmic domain which are likely to mediate contact with α-actinin are well conserved between species, suggesting that they serve an important function [23]. Connections with the cytoskeleton determine cell surface distribution of ICAM-1 and recruitment to points of interaction with other cells. This is likely to be important for optimizing and stabilizing intercellular interactions and is illustrated by the finding that contact between ICAM-1 on T- and LFA-1 on B-lymphocytes results in clustering of ICAM-

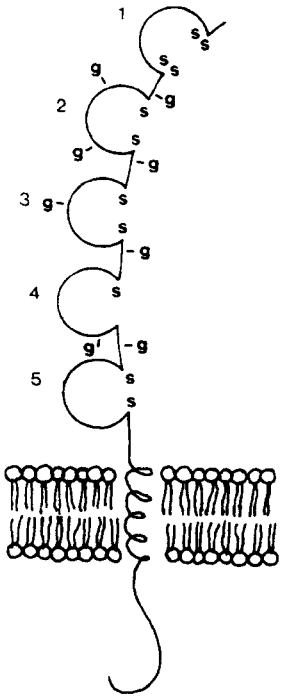

Fig. 1 Proposed structure of ICAM-1. ICAM-1 consists of a series of five Ig-like domains (*1–5*), a transmembrane domain, and a cytoplasmic tail. Each Ig domain contains 90–100 amino acids consisting of two sheets of antiparallel β strands. Cysteines in B and F β strands (*s*, sulphur atom) form disulfide bands, except for the fourth domain, which may be stabilized by hydrophobic amino acids or α disulfide band with α cysteine in flanking β strands. *g*, Eight N-linked glycosylation sites. The tertiary structure shows a slightly bent rodlike structure of 18.7 nm and ellipsoid Ig-like domains, extending 4 nm parallel to the β strand and 2.5 nm in the two perpendicular dimensions [25, 26]

1 on the area of cell-cell contact [32]. In addition, clustering of ICAM-1 on endothelial cell projections is required for binding the soluble ligand fibrinogen (see "Regulation of ligand binding") [33]. An interesting possibility associated with clustering of ICAM-1 is facilitation of outside-in signaling (see "Function").

Ligand binding

Both cell-associated and soluble ligands of ICAM-1 have been described. ICAM-1 binds to two integrins belonging to the β_2 subfamily, i.e., CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1), both expressed by leukocytes [28, 34–36]. Another less well characterized membrane receptor for ICAM-1 is CD43 (sialophorin) which is abundantly expressed by leukocytes and platelets [37, 38]. However, it is unclear to what extent CD43 contributes to ICAM-1 mediated adhesion [39]. The aminoterminal first Ig-like domain of ICAM-1 is responsible for binding to LFA-1 [26]. However, accessibility of this epitope may depend on an additional (glycosylated) epitope on Ig-like domains 4 and 5 [25, 40, 41]. On LFA-1 the ICAM-1-binding site is located on domain 5 and 6 of the CD11a subunit [42]. The third Ig-like domain of ICAM-1 mediates binding to Mac-1 [35]. However, only a subpopulation of Mac-1 binds effectively to ICAM-1 [36]. The structure of ICAM-1 probably allows both LFA-1 and Mac-1 to bind to ICAM-1 simultaneously [25].

In addition to promoting cell-cell adhesion ICAM-1 also serves as receptor for soluble fibrinogen and for the extracellular matrix factor hyaluronan [43, 44]. The fibrinogen-binding domain seems to be at least partially located in the first aminoterminal domain of ICAM-1, as determined by inhibition of binding by monoclonal antibodies, but is distinct from the LFA-1-binding epitope [43, 45, 46]. On fibrinogen the ICAM-1 binding site is located on the γ chain [45].

Human ICAM-1 also functions as receptor for the major group of rhinoviruses [47–49] and for the coxsackie A13 virus [50]. The binding domain partially overlaps with the binding site for LFA-1 [26, 27]. One additional epitope within the first aminoterminal Ig-like domain of human ICAM-1 has been characterized as the binding site of *Plasmodium falciparum* infected erythrocytes [51–53].

Of the various epitopes only the LFA-1-binding site appears to be highly conserved between species, pointing to LFA-1 as the most important ligand in vivo [23, 26, 53].

Regulation of ligand binding

LFA-1 and Mac-1 need to be activated to expose a high affinity ICAM-1 binding epitope, and binding to ICAM-1 is dependent on the presence of divalent cations [18, 28, 36, 54]. The change of LFA-1 into a high avidity state for ICAM-1 is induced by binding to ICAM-1, cross-linking of the T-cell receptor, activation of protein kinase C or increased intracellular calcium concentration, and inhibited by cAMP [18, 55–57]. In addition, activation of either ICAM-3 or CD45 (leukocyte common antigen) on leukocytes enhances LFA-1-avidity for ICAM-1 [58, 59]. The change in avidity is probably mediated by phosphorylation of the cytoplasmic domain of the β chain, resulting in a conformational change in the extracellular part of the LFA-1 molecule [55]. Interestingly, binding of LFA-1 to ICAM-2 and ICAM-3 requires similar activation of LFA-1 [12, 39], suggesting common or overlapping mechanisms to regulate interaction between this integrin and the different ICAMs.

Fibrinogen–ICAM-1 binding requires the presence of divalent cations [43], which probably induce the proper binding conformation of fibrinogen. Interestingly, fibrinogen adhered exclusively to ICAM-1 clustered on cell projections of endothelial cells and was inhibited in a reversible manner by protein kinase C mediated redistribution of F-actin [33]. We hypothesized that binding of fibrinogen to ICAM-1 may require a double adhesive bond between the two ICAM-1-binding sites on the dimeric fibrinogen molecule and two cytoskeleton-bound ICAM-1 molecules on the endothelial cell, suggesting a minimal "threshold" density of ICAM-1 to ensure fibrinogen binding.

Whether affinity of ligand-binding domains on the ICAM-1 molecule can be modified remains to be established. Cell-specific differences in carbohydrate content of ICAM-1 suggest glycosylation as a possible mechanism for affinity regulation [14]. Posttranslational modification of ICAM-1 induced by superoxide and platelet-activating factor may involve such a mechanism [60, 61]. N-Linked glycosylation has been reported to reduce the affinity of ICAM-1 for Mac-1, presumably by shielding the ligand binding epitope [35]. In contrast, glycosylation of ICAM-1 seems to have no effect on binding of LFA-1, rhinovirus, or malaria-infected erythrocytes [35, 62]. In endothelial cells tumor necrosis factor (TNF) α induces an increase in sialic acid residues on ICAM-1 [63], which may influence affinity of binding epitopes by conferring a negative charge. However, removal of sialic acid residues from ICAM-1 has been found not to influence binding to LFA-1 and Mac-1 [35]. An alternative possibility which remains to be explored is whether association of ICAM-1 with cytoskeletal proteins such as α-actinin [29] induces changes in ICAM-1 conformation and ligand affinity.

Expression regulation

Immunohistochemical studies have revealed ICAM-1 expression on endothelial and epithelial cells, macrophages, fibroblast-like cells, and dendritic cells in human thymus, lymph nodes, intestine, skin, kidney, and liver [14]. On hemopoietic cells ICAM-1 is expressed on bone marrow progenitors [64], on cells from the lymphoid lin-

Table 1 Stimulatory and inhibitory factors regulate ICAM-1 expression in a cell type specific manner. The indicated cell type can be either a primary culture or a cell line. (*A* Acute myeloid leukemia blast cells, *AC* adenocarcinoma, *BL* B-lymphocyte, *E* endothelial, *EI* endocrine islet, *EO* eosinophil, *EP* epithelial, *F* fibroblast, *G* glioma/glioblastoma, *H* hepatocyte, *K* keratinocyte, *M* monocyte, *MA* mast cell, *ME* melanoma, *MP* macrophage; *N* neuronal/neuroblastoma, *S* sarcoma, *SM* smooth muscle, *T* thyroid/thyroid carcinoma, *TC* teratocarcinoma)

ICAM-1 inducing factors	
Tumor necrosis factor-α	AC [71], E [72–75], EI [76], EP [77–79], F [14, 80], H [81], K [82], M [69, 70], N [83], S [71], SM [84, 85], T [86]
Interferon-γ	AC [71], E [73, 87], EO [88], EP [77, 89], F [14, 90], H [81], M [69, 70, 91], EI [76], EP [77, 79, 89], S [71], T [86]
Interleukin-1	AC [71], E [72, 87], EP [78], F [14], H [81], M [92], S [71]
Interleukin-3	EO [93, 94]
Interleukin-4	BL [95], F [90], M [92], MA [96]
Interleukin-5	EO [93, 94]
Interleukin-6	E [81, 97], H [81]
Thrombin	E [98, 99]
Endothelin 1–3	E [100]
Platelet-derived growth factor	SM [101]
Substance-P	E [102]
GM-CSF	EO [93, 94], A [103]
Retinoic acid	F [104], G [104–106], ME [107], N [106, 108], T [86], TC [106, 109]
Estradiol	E [110]
Cytomegalovirus	EP [89, 111]
Parainfluenza virus	EP [112]
Shear stress	E [113, 114]
Ultraviolet A	E [115]
12-*O*-Tetrade anoylphorbol-13-acetate	E [72, 75, 116], EO [88], EP [79], M [117], MP [117]
cAMP	G [105]
Lipopolysaccharide	E [72], EP [77]
Histamine	EP [118], K [82]
Oxidized low-density lipoprotein	E [119, 120]
Metal ions (Ni^{2+} and Co^{2+})	E [121]
IgM cross-linking	BL [95]
H_2O_2	E [122]
ICAM-1 inhibitory factors	
Interleukin-4	E [123]
Interleukin-10	M [91]
Transforming growth factor-β	F [104]
Glucocorticoids	AC [71], EP [117], F [80], E [124], EO [125], M [117], MP [117]
Nicotinamide	E [126], T [127]
Uncharacterized serum protein	M [69, 70, 128]

eage, and on cells from the myeloid lineage up to myelocyte and erythroblast stage, while ICAM-1 remains expressed in the monocytic lineage [14, 16, 17, 65–70]. On other cell types which do not constitutively express ICAM-1, the expression of ICAM-1 can be induced. Many agents have been described to up- or downregulate ICAM-1 expression, including cytokines, steroid hormones, and physical factors (Table 1). TNFα, interferon (IFN) γ and interleukin (IL) 1 are the most universal inducers of ICAM-1, while glucocorticoids may prove to be the most important inhibitory agents [117, 129].

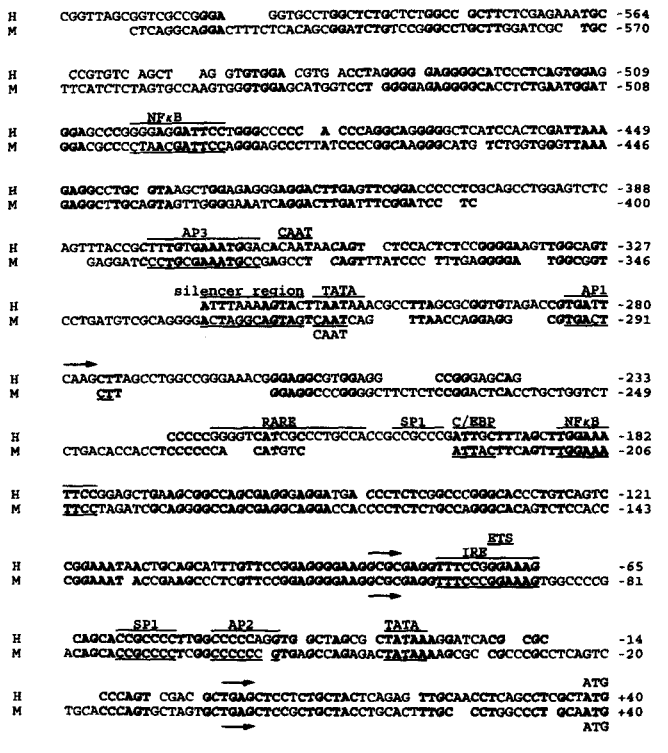

Fig. 2 The 5′ promoter region of the human (*H*) and mouse (*M*) ICAM-1 gene. *Bold*, homologous nucleotides; line over *H*, (*M*), (putative) enhancer sequences of the respective sequence: *arrows*, transcription initiation sites. ATG indicates start 1st exon

Regulation of ICAM-1 expression occurs in a cell-specific way [73, 130–132] and depends on availability of specific receptors for extracellular signals, activity of signal transduction pathways, and availability of required transcription factors. This is illustrated by observed differences in ICAM-1 promoter activity between cell types, even between cell lines derived from the same cell type [24, 132–134]. Similarly, not all endothelial and epithelial cell types express ICAM-1 in vivo, for example, portal veins and arteries in the liver [14] and gastric epithelial cells [135]. Differences in posttranscriptional machinery and activity of glycosylation enzymes add further to the cell specificity of ICAM-1 protein expression. This suggests that results obtained in cell lines and in primary cultures, such as human umbilical vein endothelial cells and monocytes, should be extrapolated to the in vivo situation only with caution [69, 70, 131].

Signal transduction pathways involved

Intracellular signal transduction pathways involved in regulation of ICAM-1 expression function in a cell type specific way. These include the intracellular second messengers protein kinase C [136], cAMP, [105, 137], Ca^{2+} [138], phospholipase A_2 [101], and the proteasome

Table 2 NFκB transcription factor complexes from several stimulated cell lines which have been shown to bind to the κB enhancer in the ICAM-1 promoter. Cell lines: *Hep G2* human hepatoma, *Mel Juso* human melanoma, *THP-1* human monocytic, *HUVEC* human umbilical vein endothelial cells

Cell line	Stimulatory factor	NFκB complexes	Reference
THP-1	TNFα	NFKB1/RelA[b] RelA[b]	
Hep G2	TNFα	NFKB1/RelA RelA/RelA	[150]
Mel Juso	TNFα	NFKB1/RelA RelA/c-Rel	[151]
THP-1	Lipopolysaccharide	RelA/c-Rel or RelA/RelA[a]	[160]
HUVEC	IL1β	NFKB1/RelA RelA/c-Rel or RelA/RelA[a]	[160]
HUVEC	TNFα	NFKB1/RelA RelA/RelA	[157]

[a] Nature of the complexes has not been confirmed by antibody-induced supershift in EMSA
[b] Wissink S, Stolpe A van de, Caldenhoven E, Saag P van der, unpublished results

[139]. Of the many known protein kinase C isotypes, protein kinase C α has been shown to mediate 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced ICAM-1 expression in A549 cells [136]. cGMP [140] and tyrosin kinase(s) may play a role in downregulation of ICAM-1 expression [141]. For many ICAM-1 inducing cytokines the involved signal transduction pathways have not been identified, for example, TNFα [116, 142].

Transcriptional regulation

Expression of ICAM-1 is regulated predominantly at transcriptional level. Northern blots detect two ICAM-1 mRNA bands, one of 3.3–3.5 kb and a smaller less abundant one of around 1.9 kb [24, 25, 117]; the significance of the two transcripts is unknown. They do not give rise to different ICAM-1 proteins, and their regulation is tightly coupled (our unpublished results) and not the result of alternative splicing or differential use of transcription initiation sites [24].

The 5′ region flanking the human ICAM-1 gene has been characterized by several groups and contains a variety of putative regulatory enhancer elements, in addition to two TATA boxes and three transcription initiation sites, suggesting complex transcription regulation [24, 143–145]. The transcription initiation sites may be used differentially depending on cell type and stimulus [24]. In addition, the first intron has been sequenced and found to contain several other putative enhancer elements, among which two κB-like elements (at +237 GGGGATTGCC and +773 GGGGAAGTCC) and an Sp1 sequence (at +458 GGGCGG) [143]. Comparison between mouse [146] and human ICAM-1 5′ promoter regions reveals areas of high homology, which are likely to harbor sequences of interest for regulation of ICAM-1 transcription (Fig. 2).

Enhancer sequences in the ICAM-1 promoter

Sp1 sites [147] probably regulate constitutive ICAM-1 transcription and elimination of the Sp1 site at –59 resulted in a significant drop in basal promoter activity ([129] and our unpublished results).

The AP1-like enhancer sequence plays a role in TPA- and TNFα-induced ICAM-1 transcription and is not identical to the consensus AP1 sequence [148], which is reflected in different binding characteristics towards members of the AP1 transcription factor family [129]. At least in some cell types this sequence appears to be coupled functionally to the distal TATA box and to initiate TPA-induced transcription through the second transcription initiation site, located close to this TATA box at –279 [24, 129].

IL6 and IFNγ regulate ICAM-1 transcription through a shared palindromic sequence, designated pIRE. Both IL6 and IFNγ induce binding of the same transcription factor, probably related to p91 signal transducer and activator of transcription 1 (STAT-1 or INFγ-activating factor), while in addition IL6 induces binding of signal transducer and activator of transcription 3 (STAT-3) to this sequence [134, 149–152].

The retinoic acid response element has been shown to be transactivated by the retinoic acid receptor (RAR) β but not by receptor isotypes RARα or RARγ [108]. However, at least for RARα, heterodimer formation with a member of the related retinoid X receptor family may be required to bind and transactivate the retinoic acid response element in the ICAM-1 promoter [107]. Interestingly, retinoic acid has also been shown to inhibit IFNγ-induced ICAM-1 transcription in monocytic cells; the mechanism behind this effect remains to be elucidated [153].

A shear stress response element is also present in the ICAM-1 promoter [154]. Although its functionality has not been demonstrated directly, this element could mediate the stimulatory effect of shear stress on ICAM-1 expression [113, 114]. Recently the AP2-like site was shown to mediate the stimulatory effect of ultraviolet A, but not ultraviolet B, on ICAM-1 transcription [155].

The κB enhancer in the ICAM-1 promoter (ICAM-κB) conveys responsiveness to TPA, TNFα, IL1, and lipopolysaccharide and probably represents the most important transcription-regulatory element in the ICAM-1

promoter [129, 156, 157]. It deviates from the consensus κB sequence [158, 159] and binds a transcription factor complex of RelA homodimers or RelA/c-Rel heterodimers in addition to the conventional nuclear factor (NF) κB transcription factor (NFKB1-RelA; Table 2; [129, 150, 151, 157, 160] and our unpublished results). Recently the proteasome, which is a protease involved in activation of NFκB, was shown to be essential for TNFα-mediated ICAM-1 expression in endothelial cells [139], providing evidence for a role of NFκB in regulation of ICAM-1 expression in vivo. One might speculate that in vivo TNFα-induced regulation of ICAM-1 transcription is determined predominantly by binding of RelA homodimers (or RelA/cRel heterodimers) to the κB element, since the affinity of ICAM-κB for NFKB1/RelA is probably too low to compete in vivo with more "classic" NFKB1/RelA binding enhancer sequences, for example, in the human immunodeficiency virus long terminal repeat, the MHC class I gene, and the Igκ light-chain enhancer [158].

In view of a number of interactions reported between members of the NFκB transcription factor family and other transcription factor families [161–163], it seems likely that different κB/Rel proteins involved in ICAM-1 transcription are part of a regulatory network, mediating cell-specific synergistic and inhibitory interactions with other cytokines/hormones. Indeed, the glucocorticoid receptor physically interacts specifically with the RelA subunit of the NFκB complex, causing inactivation of this transcription factor [129, 164–166]. The inhibitory effect of glucocorticoids on ICAM-1 transcription thus depends on the presence of RelA in the transactivating NFκB complex [165]. Similar interactions between members of the κB/Rel family and other steroid receptors have not been described. However, in vitro the progesterone receptor has been shown to repress, and RARα to enhance transactivation of ICAM-κB [165].

AP1 proteins c-Fos and c-Jun have been described to act synergistically with NFκB to transactivate a κB enhancer element or an AP1 site [161]. With respect to ICAM-κB we similarly found a synergistic effect between c-Jun and RelA, but not between c-Fos and RelA (E. Caldenhoven and P. T. van der Saag, unpublished results). A reciprocal synergistic effect on the AP1-like site in the ICAM-1 promoter is unlikely since c-Fos and c-Jun do not bind to this nonconsensus enhancer [129].

The C/EBP (NF-IL6) family of transcription factors is activated by inflammatory cytokines and may interact with κB/Rel proteins [162, 167]. A C/EBP binding site has been identified in the ICAM-1 promoter close to the ICAM-κB site and participates in TNFα-induced transcription [150]. This suggests the possibility of synergistic interaction, despite the position of the C/EBP site on the opposite DNA strand.

Cooperative interaction between NFκB and Sp1 is dependent on close association of enhancer sites [163], as is the case on the ICAM-1 promoter. However, it remains to be determined whether functional interaction plays a role in ICAM-1 transcription.

The relevance of interactions between members of the κB/Rel family and other transcription factor families for regulation of ICAM-1 transcription remains to be established. Such a network of interactions conceivably adds much to the already complex regulation of ICAM-1 expression in vivo and may provide clues to explain cell-specific regulation. In the future, additional enhancer sequences are likely to be identified in the ICAM-1 promoter, especially in evolutionary conserved regions and in the first intron.

Posttranscriptional regulation

While transcriptional regulation probably accounts for most regulatory effects on ICAM-1 expression, TPA and IFNγ may also upregulate ICAM-1 expression by stabilizing mRNA [75]. This mechanism may be particularly relevant in cells that constitutively express low ICAM-1 levels due to a short half-life of mRNA, for example, endothelial cells. The 3′ untranslated region of ICAM-1 mRNA contains multiple destabilizing AUUUA sequences, which act as target for the mRNA-stabilizing effect of TPA [168, 169]. Surprisingly, IFNγ stabilizes ICAM-1 mRNA through a "response element" located in the region encoding the cytoplasmic domain of ICAM-1 [169].

The extremely rapid increase in ICAM-1 dependent leukocyte adhesion to endothelial cells by factors such as leukotriene B_4 [170], thrombin [98], platelet activating factor [60], and the nitric oxide inhibitor N^G-nitro-L-arginine methyl ester [60] occurs without a measurable increase in ICAM-1 expression and may therefore be due to rapid posttranslational modification of ICAM-1, for example, changes in glycosylation associated with increased ligand binding (see "Regulation of ligand binding") [60, 61, 171].

Yet another way to regulate availability of ICAM-1 on the cell surface may be proteolytic cleavage, resulting in release of the extracellular part of ICAM-1 as soluble ICAM-1 (see "Soluble ICAM-1").

Function

Mice, in which the gene coding for ICAM-1 is inactivated by homologous recombination in embryonal stem cells and crossing of heterozygotic animals, develop normally and are viable. However, blood neutrophil counts are increased [20] while activation and migration of leukocytes to places of inflammation are reduced, resulting in a deficient inflammatory reaction [19]. On the other hand, the absence of ICAM-1 seems to protect mice against lethal septic shock induced by bacterial lipopolysaccharide by reducing leukocyte-endothelial cell interaction [20]. In thymic organ culture ICAM-1 was found to be required for normal T-lymphocyte maturation [172], but this was not confirmed in ICAM-1 knock-out mice [136]. However, together, these experiments suggest an important immunological function for

ICAM-1, as well as a pathophysiological role in septic shock.

The basic function of ICAM-1 is the induction of specific and reversible cell-cell adhesion, resulting in intercellular communication. Adhesion can be modulated by changes in both affinity and expression of ICAM-1 and its counter-receptor. For example, short-term adhesive interactions between cytotoxic T-cells and target cells probably depend on changes in avidity of LFA-1 and Mac-1 for ICAM-1 [18, 36, 54] (see "T-Lymphocyte activation"). On the other hand, changes in ICAM-1 expression are more likely to contribute to relatively long-term adhesion processes, for example, adhesion of leukocytes to endothelial cells (see "Leukocyte-endothelial cell interaction").

In addition to the adhesive function of ICAM-1, outside-in signaling through ICAM-1 has been studied by cross-linking ICAM-1 on the cell surface using monoclonal antibodies (mAbs). This may lead to inhibition of cytokine release (e.g., IFNγ, TNFα, and IL1) from activated lymphocytes [173] and induction of an oxidative burst in monocytes [174]. In brain endothelial cells activation of the kinase $pp60^{src}$ has been described upon ICAM-1 cross-linking, which is associated with phosphorylation of several target proteins, among which the cytoskeleton-binding protein cortactin [175]. Co-cross-linking of membrane IgM and ICAM-1 on Burkitt lymphoma cells interfered with calcium mobilization, induced by cross-linking of IgM alone [176]. Thus, evidence has accumulated that following cell-cell adhesion ICAM-1 itself may have a signaling function. With regard to this, it is interesting that ICAM-3 has similarly been shown to transduce signals into the cell and to induce changes in intracellular calcium levels and tyrosine phosphorylation [177–179].

T-Lymphocyte activation

Interaction between ICAM-1 and its counter-receptor LFA-1 plays a role in T-cell mediated host defense mechanisms and in generating an inflammatory response [3]. Within the immune system ICAM-1 is expressed on cells of the monocyte-macrophage lineage [14, 16, 69, 70], on B-lymphocytes [65] and plasma cells [68] and on both memory and activated T-lymphocytes [14, 16, 17, 66]. Activated lymphocytes demonstrate enhanced ICAM-1 expression.

Antigen-presenting cells, such as macrophages and a subset of B-lymphocytes, express ICAM-1 in association with MHC class II–antigen complex, to activate CD4-positive helper T-cells [180, 181]. Indeed, cotransfection of ICAM-1 and HLA-DR7 results in effective antigen presentation and MHC class II restricted T-cell activation [180, 182]. In cell-mediated cytotoxicity ICAM-1 plays a costimulatory role in activation of non-MHC-restricted killer cells [183, 184] and of MHC class I restricted CD8- positive cytotoxic T-lymphocytes [185–187].

Leukocyte-endothelial cell interaction

Weak transient interactions between leukocytes and cytokine-activated endothelium are mediated by members of the selectin family and result in "rolling" of leukocytes along the endothelium. Subsequent interaction between leukocyte integrins and ICAM-1 on activated endothelial cells consolidates binding and promotes spreading and locomotion of adhering cells [1, 30, 92, 188]. The Ig-like adhesion molecule platelet/endothelial cell adhesion molecule (CD31) probably plays a role in subsequent extravasation [189, 190]. Fibrinogen may enhance leukocyte adhesion and migration by functioning as a bridging molecule between Mac-1 (and possibly ICAM-1) on the leukocyte and ICAM-1 on the endothelial cell [43, 45]. The relevance of ICAM-1 for adhesion and migration of leukocytes has been convincingly demonstrated by several studies employing mAbs to ICAM-1 or antisense ICAM-1 RNA, in which leukocyte adhesion is inhibited [46, 191–193]. Interaction between adhering monocytes and endothelial cells may result in local release of ICAM-1 inducing cytokines such as TNFα and the production of tissue factor [194–196] and of chemotactic substances such as macrophage-inhibitory protein 1α [197]. Initiation of the extrinsic coagulation pathway may lead to conversion of ICAM-1 bound fibrinogen into fibrin [33], providing a potential role for ICAM-1 in hemostasis and thrombosis.

Effects on cell differentiation

A role for ICAM-1 in myeloid cell lineage differentiation has been suggested because in a mouse model ICAM-1 was rapidly and transiently expressed following differentiation-induction of myeloblasts or normal myeloid progenitor cells [198]. However, ICAM-1 seems not to be involved in the interaction of progenitor cells with bone marrow stroma, which plays an important role in differentiation [199]. A role of ICAM-1 has also been postulated in terminal megakaryocyte differentiation [200], osteoclast development [201], and prevention of apoptosis in adhering B-lymphocytes [202].

Contributions of ICAM-2 and ICAM-3 to the immune response

LFA-1 is the common ligand for ICAM-1, ICAM-2, and ICAM-3 [12], which all contribute to the immune response by providing a costimulatory signal for T-cell proliferation [39]. Specificity of LFA-1–ICAM interaction is likely to be determined by differences in cellular expression level between the ICAMs and in their affinity for LFA-1, as ICAM-1 exhibits highest and ICAM-3 lowest affinity [12, 39]. While ICAM-1 is strongly expressed by activated lymphocytes and endothelial cells, ICAM-3 is the most abundant ICAM on resting monocytes and lymphocytes, and ICAM-2 is constitutively

(and noninducably) expressed by resting endothelial cells [6–8]. This suggests a role for ICAM-2 and ICAM-3 in early recruitment of leukocytes during initiation of the immune response, before ICAM-1 expression is upregulated. In addition, ICAM-2 on endothelial cells has been suggested to take part in the recirculation of resting lymphocytes [203]. In view of the restricted expression pattern of ICAM-3 (antigen-presenting cells) and ICAM-2 (antigen-presenting cells and endothelial cells), MHC class I-restricted T cell cytotoxicity remains the sole domain of ICAM-1.

Soluble ICAM-1

A soluble form of ICAM-1 (sICAM-1) is present in plasma, as well as in cerebrospinal fluid [204] and sputum [205]. Mononuclear cells, endothelial cells, keratinocytes, hepatocytes, and melanoma cells represent sources of sICAM-1 [206–211]. The molecular weight of sICAM-1 has been found to be similar to recombinant sICAM-1 (comprising the extracellular part of ICAM-1), and lower compared to the membrane-bound form [206, 210], suggesting that the circulating form of ICAM-1 consists of most of the extracellular part of ICAM-1. Several circulating isoforms of sICAM-1 have been detected (240, 430, and >500 kDa), suggesting that sICAM-1 circulates in complexed form, either with itself or with other proteins [206, 212]. In addition, cell-type dependent ICAM-1 glycosylation may contribute to variations in molecular weight. The origin of sICAM-1 remains to be elucidated. Most likely it is split off from the membrane by proteolytic cleavage. Alternatively, it represents a splice variant of ICAM-1, lacking the membrane and intracellular part; however, no corresponding mRNA has been observed.

sICAM-1 concentrations in supernatant of human umbilical vein endothelial cells correlated with membrane expression [209]. On the other hand, cytokines (IL1, TNFα, IFNγ, but not IL6) induced increased shedding of sICAM-1 from melanoma cells [207] and keratinocytes [208]. Thus sICAM-1 levels do not necessarily reflect the extent of membrane expression and may be independently regulated.

The function of sICAM-1 has been studied using recombinant sICAM-1. sICAM-1 has been shown to bind to LFA-1 only when immobilized on a solid phase and not in circulating monomeric form [62, 213, 214]. In contrast, sICAM-1 has been reported to inhibit adhesion of monocytic cells to purified ICAM-1 [213], and sICAM from a human umbilical vein endothelial cell culture interfered with the function of membrane-associated ICAM-1 [209]. Whether sICAM-1 is able to bind LFA-1 in vivo probably depends on its form, that is, either complexed as multimers or with other proteins, or as free monomers. In addition to a possible interaction with LFA-1, sICAM-1 inhibits cellular infection by a "major group" rhinovirus (HRV54) and coxsackie A13 virus, which both use ICAM-1 as their membrane receptor [50], and inhibits replication of "major group" rhinoviruses [62, 215]. Also, monomeric sICAM-1 fragments containing only the first two N-terminal domains (nonglycosylated) are able to bind to malaria-infected erythrocytes [62]. An interesting possibility is that binding of sICAM-1 to its integrin ligands induces signal transduction by the respective integrin, resulting in a functional change of the leukocyte [197, 216].

Circulating sICAM-1 can be detected by an immunodot/blot method [212] or sandwich enzyme-linked immunosorbent assay [206]. Serum levels lie around 200 ng/ml, as measured by enzyme-linked immunosorbent assay techniques [217]. It must be kept in mind that local increases in shed ICAM-1, as in melanoma (see "Melanoma"), are not necessarily reflected in elevated serum levels of sICAM-1. In the noninflammatory state when integrin receptors for ICAM-1 are not activated, serum sICAM-1 may simply reflect the amount of membrane-associated molecule. Alternatively, in inflammatory conditions sICAM-1 and membrane-bound ICAM-1 (mICAM-1) may be differentially regulated, and sICAM-1 may compete with membrane-bound ICAM-1 for binding to activated LFA-1 and Mac-1 integrins. This may give rise to an inverse relationship between circulating sICAM-1 level and general activation of the immune system. Indeed, in *P. falciparum* malaria increased sICAM-1 concentrations are inversely correlated with the level of LFA-1 expression on lymphocytes [218], and low sICAM-1 levels have been reported in patients with acute stroke and are thought to be related to the presence of leukocytes with increased activated CD18 integrins on their surface [219].

Many studies have reported associations between elevated circulating sICAM-1 levels and disorders of inflammatory or malignant origin. Serum levels are elevated in patients with leukocyte adhesion deficiency who lack the β_2 integrin chain [206], due either to increased ICAM-1 expression associated with chronic infection or to the absence of functional LFA-1 and Mac-1 molecules to bind sICAM-1. sICAM-1 may also be elevated in patients with renal failure [220], various malignancies (non-Hodgkin lymphoma, melanoma, ovarial and breast carcinomas, gastrointestinal tumors, renal and bladder carcinoma) [217, 221], acute infectious mononucleosis [222], acute *P. falciparum* malaria [218, 223], autoimmune and viral hepatitis and alcoholic cirrhosis [211, 224], idiopathic pulmonary fibrosis [225], extrinsic allergic alveolitis [226], systemic lupus erythematosus [227], diabetes [220], and active multiple sclerosis [204, 228], in whom elevated levels have also been found in cerebrospinal fluid [204]. Increased serum and sputum levels are reported during attacks of bronchial asthma[205, 229, 230]. Increased sICAM-1 concentrations in bronchial alveolar lavage fluid have been reported in patients with chronic obstructive pulmonary disease, chronic bronchitis and sarcoidosis, probably reflecting increased ICAM-1 expression by cells present in the upper airways [225, 231, 232].

Pathophysiology

As receptor for rhinoviruses and malaria-infected erythrocytes, and in view of its important functions in the immune system, (deranged) ICAM-1 expression is likely to play a role in disease. Increased ICAM-1 expression has been implicated in a variety of disorders characterized by local or generalized inflammation. However, ICAM-1 by itself probably does not elicit an inflammatory response [233] and more likely functions as an inflammation-enhancing molecule.

On malignant cells both increased and decreased ICAM-1 expression has been reported, possibly due to dedifferentiation, or secondary to (autocrine or paracrine) release of ICAM-1 regulatory factors. The role of abnormal ICAM-1 expression in the evolution of the malignant process has not been clearly defined [234]. In general, reduced ICAM-1 expression seems to be associated with more aggressive malignant disease and a tendency to metastasize, presumably because cells can escape from immune surveillance (see "Function"). Indeed, several studies have shown a correlation between ICAM-1 expression on malignant cells and in vitro sensitivity to lymphocyte cytotoxicity [185, 235–238].

Infection with rhinovirus and *Plasmodium falciparum* malaria

Rhinoviruses are a major cause of the common cold. As rhinovirus receptor ICAM-1 is likely to play a role in infections of the upper respiratory tract. In support of this, truncated soluble ICAM-1 has been shown to inhibit viral infection of human cells in vitro [239]. ICAM-1 on endothelial cells binds a subset of *P. falciparum* infected erythrocytes [53]; however, whether ICAM-1 plays a role in the clinical evolution of this type of malaria infection remains to be demonstrated.

Melanoma

The level of ICAM-1 expression on melanoma cells correlates with risk of metastasis [221, 240, 241]. In apparent contrast to this correlation, T-cell mediated killing of melanoma cells appears to depend on expression of ICAM-1 on the tumor cell [235]. A possible mechanism to explain this controversy has been provided. Several cytokines, for example, TNFα, IL1, and IFNγ, induce shedding of ICAM-1 from melanoma cells in vitro [207, 242]. A local increase in sICAM-1 may prevent cytotoxic T-cells from attacking malignant cells, despite high levels of mICAM-1 [243]. In support of this, sICAM-1 derived from melanoma cells has been shown to inhibit non-MHC-restricted as well as MHC-restricted T-cell lysis of melanoma cells [207, 244].

Hematological malignancies

A few studies have reported low ICAM-1 expression on leukemic (acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia) cells to be associated with reduced in vitro sensitivity to lymphocyte cytotoxicity, suggesting a role for ICAM-1 in the clinical evolution of these diseases [236, 237]. Many studies have tried to link ICAM-1 expression on various malignant cell types to malignancy grade and prognosis [245]. However, only in B-cell non-Hodgkin lymphomas (B-NHL) has a correlation between ICAM-1 expression and histological subtype been established (see below). Interestingly, in lymphocytic malignancies proto-oncogenes have been described which may interfere with κB-mediated gene transcription [246–249], suggesting downregulation of ICAM-1 as part of their tumorigenic mechanism.

Malignancies of myeloid origin

ICAM-1 has been detected on blast cells from about one-third of the patients with de novo acute myeloid leukemias [67, 250], myelodysplastic syndromes, acute myeloid leukemia evolving from myelodysplastic syndromes, and chronic myeloid leukemia in acute blastic phase [67] but not in chronic phase [17]. No correlation between ICAM-1 expression and prognosis has been found [67, 250]. Interestingly, acute promyelocytic leukemic cells lack ICAM-1 expression [245]. Acute promyelocytic leukemia is characterized by the presence of the RARα-PML fusion protein, which acts as a dominant negative transcription factor [251], suggesting the possibility of negative interference with retinoic acid-induced ICAM-1 transcription.

Malignancies of lymphoid origin

In B-cell lymphoproliferative disorders high ICAM-1 expression generally seems to be associated with a more differentiated and less malignant phenotype. ICAM-1 expression in acute B-lymphocytic leukemia was undetectable [252] or variable [67]. Variable levels of expression are found in chronic B-lymphocytic leukemia [17, 65, 67, 252–254]. High levels are found in plasma cell malignancies (multiple myeloma) [17, 67, 255, 256] and both high and low levels in the well-differentiated hairy cell leukemia [17, 186]. INFα therapy in patients with chronic B lymphocytic leukemia results in induction of ICAM-1 associated with clinical improvement [257]. The same has been described in a patient with hairy cell leukemia, in which the level of ICAM-1 expression was correlated with susceptibility to T-cell-mediated cytolysis [186].

In B-NHL high ICAM-1 expression is associated with low-grade follicular B-NHL, while low ICAM-1 expression occurs in highly malignant diffuse B-NHL and is

associated with bone marrow infiltration [258] or localization of malignant cells in peripheral blood [259, 260]. However, low ICAM-1 expression has also been reported in association with low-grade lymphomas, the reason for this discrepancy being unclear [67]. Low levels of ICAM-1 are usually found in highly malignant Burkitt lymphoma, although expression may be higher in Epstein-Barr virus carrying cells [17, 252, 261–263]. In general, results suggest that in B-NHL high ICAM-1 expression may enhance attachment of lymphoma cells to follicular dendritic cells (and to each other) and prevent diffuse spread of the disease [17, 238, 260]. It is not known whether the level of ICAM-1 expression on B-NHL cells is linked to differentiation stage, or whether it is determined predominantly by ICAM-1 inducing cytokines from cells infiltrating in the tumor. High ICAM-1 expression found on endothelial cells of solitary lymphomas suggests that local cytokine production may at least contribute to the increased ICAM-1 expression [264, 238]. Similarly, in Hodgkin's disease local cytokine production (e.g., by infiltrating lymphocytes) probably plays a role in stimulating ICAM-1 expression, which is high on several cell types present in Hodgkin's disease lesions, irrespective of histological subtype [265].

In contrast to B-cell malignancies, in T-cell malignancies ICAM-1 is either undetectable or variable, and no correlation with prognosis has been observed [17, 65, 67, 266].

Allergic asthma

Asthma is now being recognized as an inflammatory disorder, characterized by infiltrating inflammatory cells, for example, eosinophils, which adhere to and damage bronchial epithelium, resulting in airway hyperreactivity [267]. In asthmatic patients ICAM-1 is expressed by bronchial epithelial cells, as well as by eosinophils and macrophages obtained from sputum, nasal polyps, or bronchoalveolar lavage [31, 268]. In addition, alveolar macrophages from allergen-challenged patients produced TNFα, which in vitro induced ICAM-1 on endothelial cells [269]. Increased bronchial epithelial ICAM-1 expression probably predisposes to viral infections of the upper airways (see "Infection with rhinovirus and *Plasmodium falciparum* malaria"), which amplify inflammation and precipitate asthmatic attacks [270]. In addition, infection by parainfluenza virus type 2 may contribute directly to increased bronchial epithelial ICAM-1 expression [112]. In a primate model of asthma ICAM-1 expression has been found to be increased on bronchial epithelium, and mAbs to ICAM-1 prevented eosinophil infiltration in the airways as well as symptoms of bronchial hyperreactivity [271]. Taken together, a role for increased ICAM-1 expression in the evolution of asthmatic disease seems by now fairly well established. This may in part explain the beneficial effect of (inhalation) glucocorticoids, which downregulate ICAM-1 on bronchial epithelial cells and cells of the monocyte-macrophage lineage [117, 129, 165].

Autoimmune disorders

Increased ICAM-1 expression has been observed in rheumatoid arthritis [272], vasculitis [273], type-1 diabetes [76], sarcoidosis [231, 274, 275], lupus nephritis [276] and other forms of autoimmune glomerulonephritis [277, 278], and autoimmune thyroid disease [127]. ICAM-1 was increased in autoimmune hepatitis and chronic active hepatitis, and treatment with IFNα resulted in clinical improvement, associated with a reduction in ICAM-1 expression [279–283]. Increased ICAM-1 expression may be the consequence of infiltrating cytokine-producing leukocytes and modify the clinical course of autoimmune diseases by enhancing T-lymphocyte mediated cytotoxicity.

Atherosclerosis

Inflammatory cytokines such as TNFα and IL1 [284], oxidized low-density lipoprotein [285], and increased shear stress [136] may contribute to increased ICAM-1 expression commonly found in atherosclerotic plaques [286–290]. Increased endothelial ICAM-1 expression may contribute to fibrinogen deposition and monocyte attachment, followed by subendothelial migration [43, 45], which represents a crucial event in the development of atherosclerotic lesions [291].

Ischemia and reperfusion injury

Reperfusion of ischemic tissues results in local damage, probably caused by abnormal endothelial adhesion of leukocytes [292]. Enhanced ICAM-1 expression on postischemic endothelial cells has been shown to be at least in part responsible for this reperfusion defect [292, 293]. Both hypoxia and postischemia reperfusion are associated with increased production of oxygen radicals [171, 294]. Superoxide may inactivate nitric oxide, and together with cytokines such as platelet activating factor [171], IL1, or IL8 [294] induce a rapid increase in ICAM-1 dependent leukocyte adhesion and inflammatory damage. Indeed, using intravital video-microscopy in a mouse model, mAbs against ICAM-1 (and its ligand Mac-1) inhibited postischemic leukocyte-endothelial adhesion in postcapillary venules and prevented leakage of macromolecules [295].

Septic shock

In gram-negative bacterial infections potent inducers of ICAM-1 expression (e.g., TNFα, IL1 and lipopolysaccharide) are released into the circulation [20, 296]. Enhanced endothelial ICAM-1 expression may play a role in neutrophil extravasation, leading to abnormal endothelial permeability, pulmonary edema, and septic shock [20, 297]. In addition, we hypothesize that fibrinogen

binding to ICAM-1 on TNFα-activated endothelial cells may be involved in the sepsis-associated complication of diffuse intravascular coagulation (see "Leukocyte-endothial cell interaction") [33, 296]. Supporting a role for ICAM-1 in the development of endotoxin shock, ICAM-1 deficient mice are resistant to lipopolysaccharide -induced shock, despite elevated levels of IL1 and TNFα [20] (see "Function").

Gram-positive *Staphylococcus aureus* infections may also cause septic shock, due to the presence of *S. aureus* enterotoxins (A/B). In an experimental model ICAM-1 deficient mice were protected from death caused by administration of *S. aureus* enterotoxin B superantigen [20]. In contrast to endotoxin shock, however, this was associated with significantly lower levels of TNFα and IL1 [20], probably reflecting reduced T-cell activation in the absence of ICAM-1 [180].

Inflammatory dermatoses

Inflammatory dermatoses and allergic skin reactions are characterized by increased ICAM-1 expression on keratinocytes [298, 299]. However, transgenic mice which overexpress ICAM-1 in keratinocytes do not show an inflammatory phenotype [233]. This suggests that increased ICAM-1 expression is secondary to cutaneous inflammation and is due to infiltration of the skin by activated monocytic or lymphocytic cells [298].

Neurological disorders

In various neurological disorders resident central nervous system cells express ICAM-1 [300–303], which may contribute to local inflammatory reactions by attracting leukocytes [83]. In Alzheimer's disease ICAM-1 accumulates in senile plaques [301, 304]. In patients with multiple sclerosis ICAM-1 expression is increased on endothelial cells in "active" multiple sclerosis lesions [300, 305], which may be due to cytokine-producing lymphocytes [303].

Allogeneic organ transplantation

T-cells can react with allogeneic MHC class I molecules that do not present antigen, as occurs after allogeneic organ transplantation. Loss of the graft is due to T-cell cytotoxicity, in which ICAM-1 on cells of the transplanted tissue plays a role [306, 307]. ICAM-1 expression on graft cells may conceivably be increased by ischemia and reperfusion injury, for example, in kidney transplantation, and by cytokine release from infiltrating leukocytes. In bone marrow recipients with imminent graft-versus-host disease increased ICAM-1 expression on keratinocytes has been found, which may contribute to graft-versus-host disease [298, 308].

Therapeutic options: modifying leukocyte adhesion

Leukocyte adhesion can be inhibited by mAbs to ICAM-1 or its integrin receptors (LFA-1, Mac-1), by soluble fragments of ICAM-1 which compete with membrane-bound ICAM-1, or by inhibiting ICAM-1 expression with antisense oligonucleotides [309]. Synthetic peptides which occupy or shield relevant binding domains on ICAM-1 may also act as functional antagonists of ICAM-1 [40].

Since monomeric soluble ICAM-1 is likely to be an ineffective competitor for LFA-1, coupling of sICAM-1 to an Ig, resulting in a dimeric ICAM-1 adhesion molecule, may constitute a novel approach to create a more effective adhesion blocker. Such a chimeric molecule has already been demonstrated to block in vitro antigen-specific T-cell proliferation [310].

Systemically administered mAbs against ICAM-1 may have applications in preventing allograft rejections, graft-versus-host disease, and autoimmune diseases, while local administration of mAbs or sICAM-1 may offer possibilities to treat allergic asthma and to prevent rhinovirus infections [50, 239]. In animal models for autoimmune-mediated acute myocarditis or neuritis in vivo administration of mAbs against ICAM-1 has been shown to reduce inflammation [311, 312]. In a primate model of allergic asthma the administration of mAbs against ICAM-1 ameliorated bronchial hyperreactivity [271]. Cardiac allograft survival was prolonged in mice by the use of mAbs against either LFA-1 or ICAM-1, and prolonged graft tolerance was induced by a 6-day course of both antibodies combined [306]. Only preliminary data are available on the use of mAbs in humans. A phase I clinical trial employing a mAb to ICAM-1 in kidney transplant patients showed a tendency to increased graft survival in patients with adequate antibody levels [307]. Treatment of patients with anti-LFA-1 mAb allowed grafting with bone marrow from non-HLA-identical donors [313].

In contrast to therapeutic measures to inhibit ICAM-1 mediated adhesion, induction of ICAM-1 on tumor cells may prove to be useful to enhance tumor-directed T-cell cytotoxicity. This may be part of the mechanism by which tumor necrosis is induced after locoregional perfusion with TNFα [314]. Specific drug delivery to ICAM-1 bearing cells may also offer interesting options, for example, in the case of (metastasized) melanoma or in myeloma. Recently a mAb to ICAM-1, coupled to a ricin A-chain, was shown to be cytotoxic to human myeloma cell lines [315]. An alternative approach is to incorporate ICAM-1 mAbs into liposomes which function as drug carrier [316].

Prospects to the future

In recent years interest in ICAM-1 has been on the rise. This is due to the expectation that ICAM-1 will prove to

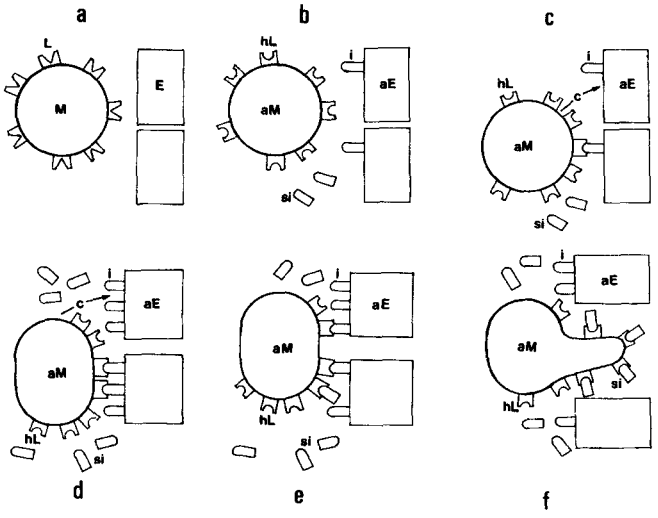

Fig. 3a–f Hypothetical model illustrating how interplay between membrane-bound ICAM-1 (mICAM-1) and soluble ICAM-1 (sICAM-1) may facilitate adhesion and migration of activated monocytes. **a,b** Elevated concentrations of cytokines such as TNFα cause activation of monocytes (*aM*) and endothelial cells (*aE*), associated with increased expression of mICAM-1 (*i*), and induction of high affinity LFA-1 (*hL*) receptors on monocytes. **c** Shedding of sICAM-1 (*si*) increases but does not interfere with adhesion of monocytes to endothelial cells due to rapid dilution in the circulation. **d** Cytokine (*c*) production by the activated adhering monocyte (e.g., IL1 and TNFα) induces the appearance of intercellular gaps, and a local increase in ICAM-1 expression, initially resulting in strengthening of the adhesion. **e,f** A concomitant local increase in sICAM-1 causes deadhesion, migration, and extravasation of monocytes

be a new tool, both in the follow-up of disease activity and to detect metastatic cancer and relapses of hematological malignancies in an early phase (see "Pathophysiology"). In addition, ICAM-1 may represent a new target for pharmacological intervention directed at modulation of the immune system, which may be of special relevance for transplantation medicine and oncology (see "Therapeutic options: modifying leukocyte adhesion"). Whether these expectations are realized depends on more detailed knowledge of the in vivo function and regulation of mICAM-1 and sICAM-1, which have generally been studied independently of each other. In addition, most associations between deranged regulation and clinical disorders have been mostly descriptive, and except for a role of ICAM-1 in allergic asthma and graft rejection no causal relations have been established (see "Pathophysiology").

Competition between sICAM-1 and mICAM-1 for the same ligand may result in local or general interference with leukocyte function. The amount of sICAM-1, relative to mICAM-1, may determine the net effect on the known functions of mICAM-1 (see "Function"). Potential determinants of the serum concentration of sICAM-1 include mICAM-1 expression level, rate of sICAM-1 shedding, amount and character of sICAM-1-binding protein(s), blood flow, and hepatic and renal clearance rates. In contrast, tissue sICAM-1 levels are relatively independent of blood flow and clearance rates. We assume that in a normal situation serum sICAM-1 levels are too low to compete efficiently with mICAM-1 and probably do not interfere with immune function. However, a different situation could arise when cells adhere and interact at close distance, for example, during leukocyte migration (Fig. 3). Cleavage of sICAM-1 from membrane-bound ICAM-1 might directly uncouple the adhering leukocyte. However, independently of the mechanism(s) behind formation of sICAM-1, its local concentration may become sufficiently high to compete with mICAM-1, further stimulating leukocyte migration and extravasation. Similar mechanisms may play a role in the interference of sICAM-1 with local T-cell cytotoxicity.

In several clinical conditions the ratio between sICAM-1 and mICAM-1 is likely to be disturbed. Examples include Hodgkin's disease and human immunodeficiency virus infection, in which increased sICAM-1 serum concentrations may play a role in the characteristically reduced cellular immunity by binding to activated lymphocytes [265, 317]. On the other hand, relatively high serum levels of sICAM-1 may protect against the development of certain autoimmune diseases, for example, diabetes mellitus [310]. In melanoma a local increase in sICAM-1 may interfere with tumor-directed cytotoxicity [244]. Thus, increased ICAM-1 expression on malignant cells may be associated with either increased or decreased T-cell cytotoxic activity, depending on the putative role of sICAM-1.

Competition between soluble and membrane-bound adhesion molecules may present a novel mechanism to regulate activity of the immune system. However, many pieces of the puzzle are still missing. How is sICAM-1 produced, and how is it regulated? Does sICAM-1 in vivo exist as monomers or multimers or in complexes with other proteins? In what form does sICAM-1 actively compete with mICAM-1, and how is the amount of "active" sICAM-1 regulated? Is it possible to establish a ratio between "active" sICAM-1 and mICAM-1, and to relate this to activation of the immune system or to evolution of local phenomena such as tumor growth and metastasis and the atherosclerotic plaque? Answers to these questions will contribute to better understanding the biological significance of ICAM-1, and provide new targets for therapeutic intervention.

Acknowledgements We wish to thank Theo de Witte for critical reading of the manuscript. Some of the research described here was conducted in the Hubrecht Laboratory and supported by Glaxo b.r., Zeist, The Netherlands, and at the Department of Hematology, University Hospital Nijmegen.

References

1. Butcher EC (1991) Leukocyte-endothelial cell recognition: three (or more) steps to specificity and diversity. Cell 67:1033–1036
2. Dustin ML (1990) Two-way signalling through the LFA-1 lymphocyte adhesion receptor. Bioessays 12:421–427

3. Springer TA (1990) Adhesion receptors of the immune system. Nature 346:425–434
4. Takeichi M (1991) Cadherin cell adhesion receptors as a morphogenetic regulator. Science 251:1451–1455
5. Staunton DE, Dustin ML, Springer TA (1989) Functional cloning of ICAM-2, a cell adhesion ligand for LFA-1 homologous to ICAM-1. Nature 339:61–64
6. Fawcett J, Holness CLL, Needham LA, Turley H, Gatter KC, Mason DY, Simmons DL (1992) Molecular cloning of ICAM-3, a third ligand for LFA-1, constitutively expressed on resting leukocytes. Nature 360:481–484
7. Fougerolles AR de, Springer TA (1992) Intercellular adhesion molecule 3, a third adhesion counter-receptor for lymphocyte function-associated molecule 1 on resting lymphocytes. J Exp Med 175:185–190
8. Vazeux R, Hoffman PA, Tomita JK, Dickinson ES, Jasman RL, St John T, Gallatin WM (1992) Cloning and characterization of a new intercellular adhesion molecule ICAM-R. Nature 360:485–488
9. Simmons D, Makgoba MW, Seed B (1988) ICAM, an adhesion ligand of LFA-1, is homologous to the neural cell adhesion molecule NCAM. Nature 331:624–627
10. Osborn L, Hession C, Tizard R, Vassallo C, Luhowskyj S, Chi-Rosso G, Lobb R (1989) Direct expression cloning of vascular cell adhesion molecule 1, a cytokine-induced endothelial protein that binds to lymphocytes. Cell 59:1203–1211
11. Newman PJ, Berndt MC, Gorski J, White GC, Lyman S, Paddock C, Muller WA (1990) PECAM-1 (CD31) cloning and relation to adhesion molecules of the immunoglobulin gene superfamily. Science 247:1219–1222
12. Binnerts ME, van Kooyk Y, Simmons DL, Figdor CG (1994) Distinct binding of T lymphocytes to ICAM-1, -2 or -3 upon activation of LFA-1. Eur J Immunol 24:2155–2160
13. Albelda SM, Buck CA (1990) Integrins and other cell adhesion molecules. FASEB J 4:2868–2880
14. Dustin ML, Rothlein R, Bhan AK, Dinarello CA, Springer TA (1986) Induction by IL 1 and interferon-γ: tissue distribution, biochemistry, and function of a natural adherence molecule (ICAM-1). J Immunol 137:245–254
15. Rothlein R, Dustin ML, Marlin SD, Springer TA (1986) A human intercellular adhesion molecule (ICAM-1) distinct from LFA-1. J Immunol 137:1270–1274
16. Dougherty GJ, Murdoch S, Hogg N (1988) The function of human intercellular adhesion molecule-1 (ICAM-1) in the generation of an immune response. Eur J Immunol 18:35–39
17. Boyd AW, Dunn SM, Fecondo JV, Culvenor JG, Dührsen U, Burns GF, Wayryk SO (1989) Regulation of expression of a human intercellular adhesion molecule (ICAM-1) during lymphohematopoietic differentiation. Blood 73:1896–1903
18. Dustin ML, Springer TA (1989) T-cell receptor cross-linking transiently stimulates adhesiveness through LFA-1. Nature 341:619–624
19. Sligh JE, Ballantyne CM, Rich SS, Hawkins HK, Smith CW, Bradley A, Beaudet AL (1993) Inflammatory and immune responses are impaired in mice deficient in intercellular adhesion molecule-1. Proc Natl Acad Sci USA 90:8529–8533
20. Xu H, Gonzalo JA, St Pierre Y, Williams IR, Kupper TS, Cotran RS, Springer TA, Gutierrez-Ramos JC (1994) Leukocytosis and resistance to septic shock in intercellular adhesion molecule 1-deficient mice. J Exp Med 180:95–109
21. Siu G, Hedrick SM, Brian AA (1989) Isolation of the murine intercellular adhesion molecule 1 (ICAM-1) gene. J Immunol 143:3813–3820
22. Kita Y, Takashi T, Iigo Y, Tamatani T, Miyasaki M, Horiuchi T (1992) Sequence and expression of rat ICAM-1. Biochim Bioph Acta 1131:108–110
23. Manning AM, Lu HF, Kukielka GL, Oliver MG, Ty T, Toman CA, Drong RF, Slightom JL, Ballantyne CM, Entman ML, Smith CW, Anderson DC (1995) Cloning and comparative sequence analysis of the gene encoding canine intercellular adhesion molecule-1 (ICAM-1). Gene 156:291–295
24. Voraberger G, Schäfer R, Stratowa C (1991) Cloning of the human gene for intercellular adhesion molecule 1 and analysis of its 5′-regulatory region. J Immunol 147:2777–2786
25. Staunton DE, Marlin SD, Stratowa C, Dustin ML, Springer TA (1988) Primary structure of ICAM-1 demonstrates interaction between members of the immunoglobulin and integrin supergene families. Cell 52:925–933
26. Staunton DE, Dustin ML, Erickson HP, Springer TA (1990) The arrangement of the immunoglobulin-like domains of ICAM-1 and the binding sites for LFA-1 and rhinovirus. Cell 61:243–254
27. Giranda VL, Chapman MS, Rossmann MG (1990) Modeling of the human intercellular adhesion molecule-1, the human rhinovirus major group receptor. Proteins 7:227–233
28. Marlin SD, Springer TA (1987) Purified intercellular adhesion molecule-1 (ICAM-1) is a ligand for lymphocyte function-associated antigen 1 (LFA-1). Cell 51:813–819
29. Carpén O, Pallai P, Staunton DE, Springer TA (1992) Association of intercellular adhesion molecule-1 (ICAM-1) with actin-containing cytoskeleton and α-actinin. J Cell Biol 118:1223–1234
30. Dustin ML, Carpen O, Springer TA (1992) Regulation of locomotion and cell-cell contact area by the LFA-1 and ICAM-1 adhesion receptors. J Immunol 148:2654–2663
31. Vignola AM, Chanez P, Campbell AM, Pinel AM, Bousquet J, Michel FB, Godard PH (1994) Quantification and localization of HLA-DR and intercellular adhesion molecule-1 (ICAM-1) molecules on bronchial epithelial cells of asthmatics using confocal microscopy. Clin Exp Immunol 96:104–110
32. Sanders VM, Vitetta ES (1991) B cell-associated LFA-1 and T cell-associated ICAM-1 transiently cluster in the area of contact between interacting cells. Cell Immunol 132:45–55
33. Stolpe A van de, Jacobs N, Hage WJ, Tertoolen L, Kooyk Y van, Nováková IRO, Witte T de (1996) Fibrinogen-binding to intercellular adhesion molecule-1 on EA.hy 926 endothelial cells is dependent on an intact cytoskeleton. Thromb Haemost (in press)
34. Diamond MS, Staunton DE, de Fougerolles AR, Stacker SA, Garcia-Aguilar J, Hibbs ML, Springer TA (1990) ICAM-1 (CD54): a counter-receptor for Mac-1 (CD11b/CD18). J Cell Biol 111:3129–3139
35. Diamond MS, Staunton DE, Marlin SD, Springer TA (1991) Binding of the integrin Mac-1 (CD11b/CD18) to the third immunoglobulin-like of ICAM-1 (CD54) and its regulation by glycosylation. Cell 65:961–971
36. Diamond MS, Springer TA (1993) A subpopulation of Mac-1 (CD11b/CD18) molecules mediates neutrophil adhesion to ICAM-1 and fibrinogen. J Cell Biol 120:545–556
37. Remold-O'Donnell E, Zimmerman C, Kenney D, Rosen FS (1987) Expression on blood cells of sialophorin, the surface glycoprotein that is defective in Wiskott-Aldrich syndrome. Blood 70:104–109
38. Rosenstein Y, Park JK, Hahn WC, Rosen FS, Bierer BE, Burakoff SJ (1991) CD43, a molecule defective in Wiskott-Aldrich syndrome, binds ICAM-1. Nature 354:233–235
39. Fougerolles AR de, Qin X, Springer TA (1994) Characterization of the function of intercellular adhesion molecule (ICAM)-3 and comparison with ICAM-1 and ICAM-2 in immune responses. J Exp Med 179:619–629
40. Fecondo JV, Kent SBH, Boyd AW (1991) Inhibition of intercellular adhesion molecule 1-dependent biological activities by a synthetic peptide analog. Proc Natl Acad Sci USA 88:2879–2882
41. Bloemen P, Moldenhauer G, van Dijk M, Schuurman HJ, Bloem AC (1992) Multiple ICAM-1 (CD54) epitopes are involved in homotypic B-cell adhesion. Scand J Immunol 35:517–523
42. Stanley P, Bates PA, Harvey J, Bennett RI, Hogg N (1994) Integrin LFA-1 α subunit contains an ICAM-1 binding site in domains V and VI. EMBO J 13:1790–1798
43. Languino LR, Plescia J, Duperray A, Brian AA, Plow EF, Geltosky JE, Altieri DC (1993) Fibrinogen mediates leuko-

cyte adhesion to vascular endothelium through an ICAM-1-dependent pathway. Cell 73:1423–1434
44. McCourt PAG, Ek B, Forsberg N, Gustafson S (1994) Intercellular adhesion molecule-1 is a cell surface receptor for Hyaluronan. J Biol Chem 269:30081–30084
45. Altieri DC, Duperray A, Plescia J, Thornton GB, Languino LR (1995) Structural recognition of a novel fibrinogen γ chain sequence (117–133) by intercellular adhesion molecule-1 mediates leukocyte-endothelium interaction. J Biol Chem 270:696–699
46. Languino LR, Duperray A, Joganic KJ, Fornaro M, Thornton GB, Altieri DC (1995) Regulation of leukocyte-endothelium interaction and leukocyte transendothelial migration by intercellular adhesion molecule 1-fibrinogen recognition. Proc Natl Acad Sci USA 92:1505–1509
47. Greve JM, Davis G, Meyer AM, Forte CP, Yost SC, Marlor CW, Kamarck ME, McClelland A (1989) The major human rhinovirus receptor is ICAM-1. Cell 56:839–847
48. Staunton DE, Merluzzi, R. Rothlein, R. Barton, S. D. Marlin, T. A. Springer (1989) A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses. Cell 56:849–853
49. Tomassini JE, Graham D, DeWitt CM, Lineberger DW, Rodkey JA, Colonno RJ (1989) cDNA cloning reveals that the major group rhinovirus receptor on HeLa cells is intercellular adhesion molecule-1. Proc Natl Acd Sci USA 86:4907–4911
50. Marlin SD, Staunton DE, Springer TA, Stratowa C, Sommergruber W, Merluzzi VJ (1990) A soluble form of intercellular adhesion molecule-1 inhibits rhinovirus infection. Nature 344:70–72
51. Berendt AR, Simmons DL, Tansey J, Newbold CI, Marsh K (1989) Intercellular adhesion molecule-1 is an endothelial cell adhesion receptor for *Plasmodium falciparum*. Nature 341:57–59
52. Ockenhouse CF, Ho M, Tandon NN, van Seventer GA, Shaw S, White NJ, Jamieson GA, Chulay JD, Webster HK (1991) Molecular basis of sequestration in severe and uncomplicated *Plasmodium falciparum* malaria: differential adhesion of infected erythrocytes to CD36 and ICAM-1. J Inf Dis 164:163–169
53. Ockenhouse CF, Betageri R, Springer TA, Staunton DE (1992) *Plasmodium falciparum*-infected erythrocytes bind ICAM-1 at a site distinct from LFA-1, Mac-1 and human rhinovirus. Cell 68:63–69
54. Kooyk Y van, van Kemenade PV, Weder P, Kuijpers TW, Figdor CG (1989) Enhancement of LFA-1-mediated cell adhesion by triggering through CD2 or CD3 on T lymphocytes. Nature 342:811–813
55. Hibbs ML, Xu H, Stacker SA, Springer TA (1991) Regulation of adhesion to ICAM-1 by the cytoplasmic domain of LFA-1 integrin β subunit. Science 251:1611–1613
56. Cabanas C, Hogg N (1993) Ligand intercellular adhesion molecule 1 has a necessary role in activation of integrin lymphocyte function-associated molecule 1. Proc Natl Acad Sci USA 90:5838–5842
57. Kooyk Y van, Weder P, Heye K, Figdor CG (1994) Extracellular Ca^{2+} modulates leukocyte function-associated antigen-1 cell surface distribution on T lymphocytes and consequently affects cell adhesion. J Cell Biol 124:1061–1070
58. Campanero M R, del Pozo MA, Arroyo AG, Sanchez-Mateos P, Hernández-Caselles T, Craig A, Pulido R, Sánchez-Madrid F (1993) ICAM-3 interacts with LFA-1 and regulates the LFA-1/ICAM-1 cell adhesion pathway. J Cell Biol 123:1007–1016
59. Lorentz HM, Lagoo AS, Hardy KJ (1994) The cell and molecular basis of leukocyte common antigen (CD45)-triggered, lymphocyte function-associated antigen-1-/intercellular adhesion molecule-1-dependent, leukocyte adhesion. Blood 83:1862–1870
60. Niu XF, Smith CW, Kubes P (1994) Intracellular oxidative stress induced by nitric oxide synthesis inhibition increases endothelial cell adhesion to neutrophils. Circ Res 74:1133–1140
61. Sellak H, Franzini E, Hakim J, Pasquier C (1994) Reactive oxygen species rapidly increase endothelial ICAM-1 ability to bind neutrophils without detectable upregulation. Blood 83:2669–2677
62. Martin S, Martin A, Staunton DE, Springer TA (1993) Functional studies of truncated soluble intercellular adhesion molecule-1 expressed in *Escherichia coli*. Antimicrob Agents Chemother 37:1278–1285
63. Hanasaki K, Varki A, Stamenkovich I, Bevilacqua MP (1994) Cytokine-induced β-galactoside α2,6-sialytransferase in human endothelial cells mediates α2,6-sialylation of adhesion molecules and CD22 ligands. J Biol Chem 269:10637–10643
64. Liesveld JL, Dipersio JF, Abboud CN (1994) Integrins and adhesive receptors in normal and leukemic $CD34^+$ progenitor cells: potential regulatory checkpoints for cellular traffic. Leuk Lymphoma 14:19–28
65. Clark EA, Ledbetter JA, Holly RC, Dinndorf PA, Shu G (1986) Polypeptides on human B lymphocytes associated with cell activation. Hum Immunol 16:100–105
66. Buckle AM, Hogg N (1990) Human memory T cells express intercellular adhesion molecule-1 which can be increased by interleukin 2 and interferon-γ. Eur J Immunol 20:337–341
67. Maio M, Pinto A, Carbone A, Zagonel V, Gloghini A, Marotta G, Cirillo D, Colombatti A, Ferrara F, del Vecchio L, Ferrone S (1990) Differential expression of CD54/intercellular adhesion molecule-1 in myeloid leukemias and in lymphoproliferative disorders. Blood 76:783–790
68. Arkin S, Naprstek B, Guarini L, Ferrone S, Lipton JM (1991) Expression of intercellular adhesion molecule-1 (CD54) on hematopoietic progenitors. Blood 77:948–953
69. Möst J, Schwaeble W, Dierich MP (1992) Expression of intercellular adhesion molecule-1 (ICAM-1) on human monocytes. Immunobiol 185:327–336
70. Möst J, Schwaeble W, Drach J, Sommerauer A, Dierich MP (1992) Regulation of the expression of ICAM-1 on human monocytes and monocytic tumor cell lines. J Immunol 148:1635–1642
71. Rothlein R, Czajkowski M, O'Neill MM, Marlin SD, Mainolfi E, Merluzzi VJ (1988) Induction of intercellular adhesion molecule 1 on primary and continuous cell lines by pro-inflammatory cytokines. J Immunol 141:1665–1669
72. Myers CL, Wertheimer SJ, Schembri-King J, Parks T, Wallace RW (1992) Induction of ICAM-1 by TNF-α, IL-1ß, and LPS in human endothelial cells after downregulation of PKC. Am J Physiol 263:C767-C772
73. Gerritsen ME, Kelly KA, Ligon G, Perry CA, Shen CP, Szczepanski A, Carley WW (1993) Regulation of the expression of intercellular adhesion molecule 1 in cultured human endothelial cells derived from rheumatoid synovium. Arthritis Rheum 36:593–602
74. Thorp KM, Southern C, Bird IN, Matthews N (1992) Tumor necrosis factor induction of ELAM-1 and ICAM-1 on human umbilical vein endothelial cells – analysis of tumor necrosis factor-receptor interactions. Cytokine 4:313–319
75. Wertheimer SJ, Myers CL, Wallace RW, Parks TP (1992) Intercellular adhesion molecule-1 gene expression in human endothelial cells. J Biol Chem 267:12030–12035
76. Campbell IL, Cutri A, Wilkinson D, Boyd AW, Harrison LC (1989) Intercellular adhesion molecule 1 is induced on isolated endocrine islet cells by cytokines but not by reovirus infection. Proc Natl Acad Sci USA 86:4282–4286
77. Jevnikar AM, Wuthrich RP, Takei F, Xu HW, Brennan DC, Glimcher LH, Rubin-Kelly VE (1990) Differing regulation and function of ICAM-1 and class II antigens on renal tubular cells. Kidney Int 38:417–425
78. Tosi MF, Stark JM, Smith CW, Hamedani A, Gruenert DC, Infeld MD (1992) Induction of ICAM-1 expression on human airway epithelial cells by inflammatory cytokines: effects on neutrophil-epithelial cell adhesion. Am J Resp Cell Mol Biol 7:214–221

79. Bloemen PGM, van den Tweel MC, Henricks PAJ, Engels F, Wagenaar SS, Rutten AAJJL, Nijkamp FP (1993) Expression and modulation of adhesion molecules on human bronchial epithelial cells. Am J Respir Cell Mol Biol 9:586–593
80. Tessier P, Audette M, Cattaruzzi P, McColl SR (1993) Up-regulation by tumor necrosis factor α of intercellular adhesion molecule-1 expression and function in synovial fibroblasts and its inhibition by glucocorticoids. Arthritis Rheum 36:1528–1539
81. Kvale D, Brandtzaeg P (1993) Immune modulation of adhesion molecules ICAM-1 (CD54) and LFA-3 (CD58) in human hepatocytic cell lines. J Hepatol 17:347–352
82. Mitra RS, Shimizu Y, Nickoloff BJ (1993) Histamine and *cis*-urocanic acid augment tumor necrosis factor-alpha mediated induction of keratinocyte intercellular adhesion molecule-1 expression. Cell Physiol 156:348–357
83. Birdsall HH, Lane C, Ramser MN, Anderson DC (1992) Induction of VCAM-1 and ICAM-1 on human neural cells and mechanisms of mononuclear leukocyte adherence. J Immunol 148:2717–2723
84. Couffinhal T, Duplàa C, Labat L, Lamaziere JMD, Moreau C, Printseva O, Bonnet J (1993) Tumor necrosis factor-α stimulates ICAM-1 expression in human vascular smooth muscle cells. Arterioscler Thromb 13:407–414
85. Couffinhal T, Duplàa C, Moreau C, Lamaziere JM, Bonnet J (1994) Regulation of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in human vascular smooth muscle cells. Circ Res 74:225–234
86. Bassi V, Vitale M, Feliciello A, Deriu S, Rossi G, Fenzi G (1995) Retinoic acid induces intercellular adhesion molecule-1 hyperexpression in human thyroid carcinoma cell lines. J Clin Endo Metab 80:1129–1135
87. Pober JS, Gimbrone Jr. MA, Lapierre LA, Mendrick DL, Fiers W, Rothlein R, Springer TA (1986) Overlapping patterns of activation of human endothelial cells by interleukin 1, tumor necrosis factor, and immune interferon. J Immunol 137:1893–1896
88. Nambu M, Mayumi M, Mikawa H (1992) Regulation of the expression of leukocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1) on a human eosinophilic leukemia cell line eol-3. Cell Immunol 143:335–347
89. Ibrahim L, Dominquez M, Yacoub M (1993) Primary human adult lung epithelial cells in vitro: response to interferon-γ and cytomegalovirus. Immunol 79:119–124
90. Piela-Smith TH, Broketa G, Hand A, Korn JH (1992) Regulation of ICAM-1 expression and function in human dermal fibrolasts by IL-4. J Immunol 148:1375–1381
91. Willems F, Marchant A, Delville JP, Gérard C, Delvaux A, Velu T, de Boer M, Goldman M (1994) Interleukin-10 inhibits B7 and intercellular adhesion molecule-1 expression on human monocytes. Eur J Immunol 24:1007–1009
92. Beekhuizen H, Verdegaal EME, Blokland I, van Furth R (1992) Contribution of ICAM-1 and VCAM-1 to the morphological changes in monocytes bound to human venous endothelial cells stimulated with recombinant interleukin-4 (rIL-4) or rIL-1α. Immunol 77:469–472
93. Czech W, Krutmann J, Budnik A, Schöpf E, Kapp A (1993) Induction of intercellular adhesion molecule 1 (ICAM-1) expression in normal human eosinophils by inflammatory cytokines. J Invest Dermatol 100:417–423
94. Hansel TT, de Vries IJM, Carballido JM, Braun RK, Carballido-Perrig N, Rihs S, Blaser K, Walker C (1992) Induction and function of eosinophil intercellular adhesion molecule-1 and HLA-DR. J Immunol 149:2130–2136
95. Brändén H Lundgren E (1993) Differential regulation of LFA-1 and ICAM-1 on human primary B-lymphocytes. Cell Immunol 147:64–72
96. Valent P, Bevec D, Maurer D, Besemer J, di Padova F, Butterfield JH, Speiser W, Majdic O, Lechner K, Bettelheim P (1991) Interleukin 4 promotes expression of mast cell ICAM-1 antigen. Proc Natl Acad Sci USA 88:3339–3342
97. Ohteki T, Okamoto S, Nakamura M, Nemoto E, Kumagai K (1993) Elevated production of interleukin 6 by hepatic MNC correlates with ICAM-1 expression on the hepatic sinusoidal endothelial cells in autoimmune MRL/lpr mice. Immunol Lett 36:145–152
98. Palmblad JEW, Lerner R (1992) Leukotriene B_4-induced hyperadhesiveness of endothelial cells for neutrophils: Relation to CD54. Clin Exp Immunol 90:300–304
99. Sugama Y, Tiruppathi C, Janakidevi K, Andersen TT, Fenton II JW, Malik AB (1992) Thrombin-induced expression of endothelial P-selectin and intercellular adhesion molecule-1: a mechanism for stabilizing neutrophil adhesion. J Cell Biol 119:935–944
100. McCarron RM, Wang L, Stanimirovic DB, Spatz M (1993) Endothelin induction of adhesion molecule expression on human brain microvascular endothelial cells. Neurosci Letters 156:31–34
101. Morisaki N, Takahashi K, Shiina R, Zenibayashi M, Otabe M, Yoshida S, Salto Y (1994) Platelet-derived growth factor is a potent stimulator of expression of intercellular adhesion molecule-1 in human arterial smooth muscle cells. Biochem Biophys Res Commun 200:612–618
102. Nakagawa N, Iwamoto I, Yoshida S (1993) Effect of substance P on the expression of an adhesion molecule ICAM-1 in human vascular endothelial cells. Regul Peptides 46:223–224
103. Bendall LJ, Kortlepel K, Gottlieb DJ (1995) GM-CSF enhances IL-2-activated natural killer celll lysis of clonogenic AML cells by upregulating target cell expression of ICAM-1. Leukemia 9:677–684
104. Darley R, Morris A, Passas J, Bateman W (1993) Interactions between interferon γ and retinoic acid with transforming growth factor β in the induction of immune recognition molecules. Cancer Immunol Immunother 37:112–118
105. Bouillon M, Fortier MA, Boulianne R, Audette M (1992) Biphasic effect of cAMP-elevating agents on ICAM-1 expression stimulated by retinoic acid and interferon γ. Int J Cancer 50:281–288
106. Bouillon M, Audette M (1993) Transduction of retinoic acid and γ-interferon signal for intercellular adhesion molecule-1 expression on human tumor cell lines: evidence for the late-acting involvement of protein kinase C inactivation. Cancer Res 33:826–832
107. Cilenti L, Toniato E, Ruggiero P, Fusco C, Farina AR, Tiberio A, Hayday AC, Gulino A, Frati L, Martinotti S (1995) Transcriptional modulation of the human intercellular adhesion molecule gene 1 (ICAM-1) by retinoic acid in melanoma cells. Exp Cell Res 218:263–270
108. Aoudjit F, Bossé M, Stratowa C, Voraberger G, Audette M (1994) Regulation of intercellular adhesion molecule-1 expression by retinoic acid: analysis of the 5′ regulatory region of the gene. Int J Cancer 58:543–549
109. Bouillon M, Tessier P, Boulianne R, Destrempe R, Audette M (1991) Regulation by retinoic acid of ICAM-1 expression on human tumor cell lines. Biochim Biophys Acta 1097:95–102
110. Cid MC, Kleinman HK, Grant DS, Schnaper HW, Fauci AS, Hoffman GS (1994) Estradiol enhances leukocyte binding to tumor necrosis factor (TNF)-stimulated endothelial cells via an increase in TNF-induced adhesion molecules E-selectin, intercellular adhesion molecule type 1, and vascular cell adhesion molecule type 1. J Clin Invest 93:17–25
111. Dorp WT van, Wieringen PAM van, Marselis-Jonges E, Bruggeman CA, Daha MR, Es LA van, Woude FJ van der (1993) Cytomegalovirus directly enhances MHC class 1 and intercellular adhesion molecule-1 expression on cultured proximal tubular epithelial cells. Transplantation 55:1367–1371
112. Tosi MF, Stark JM, Hamedani A, Smith CW, Gruenert DC, Huang YT (1993) Intercellular adhesion molecule-1 (ICAM-1)-dependent adhesive interactions between polymorphonuclear leukocytes and human airway epithelial cells infected with parainfluenza virus type 2. J Immunol 149:3345–3349

113. Nagel T, Atkinson WJ, Dewey CF, Gimbrone Jr MA (1994) Shear stress selectively upregulates intercellular adhesion molecule-1 expression in cultured human vascular endothelial cells. J Clin Invest 94:885–891
114. Tsuboi H, Ando J, Korenaga R, Takada Y, Kamiya A (1995) Flow stimulates ICAM-1 expression time and shear stress dependently in cultured human endothelial cells. Biochem Biophys Res Commun 206:988–996
115. Heckmann M, Eberlein-König B, Wollenberg A, Przybilla A, Plewig G. (1994) Ultraviolet-A radiation induces adhesion molecule expression on human dermal microvascular endothelial cells. Br J Dermatol 131:311–318
116. Ritchie AJ, Johnson DR, Ewenstein BM, Pober JS (1991) Tumor necrosis factor induction of endothelial cell surface antigens is independent of protein kinase C activation or inactivation. J Immunol 146:3056–3062
117. Stolpe A van de, Caldenhoven E, Raaijmakers JAM, Saag PT van der, Koenderman L (1993) Glucocorticoid-mediated repression of intercellular adhesion molecule-1 expression in human monocytic and bronchial epithelial cell lines. Am J Respir Cell Mol Biol 8:340–347
118. Vignola AM, Campbell AM, Chanez P, Lacoste P, Michel FB, Godard P, Bousquet J (1993) Activation by histamine of bronchial epithelial cells from nonasthmatic subjects. Am J Respir Cell Mol Biol 9:411–417
119. Palkama T, Majuri ML, Mattila P, Hurme M, Renkonen R (1993) Regulation of endothelial adhesion molecules by ligands binding to the scavenger receptor. Clin Exp Immunol 92:353–360
120. Sugiyama S, Kugiyama K, Ohgushi M, Fujimoto K, Yasue H (1994) Lysophosphatidylcholine in oxidized low-density lipoprotein increases endothelial susceptibility to polymorphonuclear leukocyte-induced endothelial dysfunction in porcine coronary arteries. Circ Res 74:565–575
121. Goebeler M, Meinardus-Hager G, Roth J, Goerdt S, Sorg C (1993) Nickel chloride and cobalt chloride, two common contact sensitizers, directly induce expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule (ELAM-1) by endothelial cells. J Invest Dermatol 100:759–765
122. Lo SK, Janakidevi K, Lai L, Malik AB (1993) Hydrogen peroxide-induced increase in endothelial adhesiveness is dependent on ICAM-1 activation. Am J Physiol 264:L406-L412
123. Renkonen R, Mattila P, Majuri M-L, Paavonen T, Silvennoinen (1992) IL-4 decreases IFN-γ-induced endothelial ICAM-1 expression by a transcriptional mechanism. Scand J Immunol 35:525–530
124. Cronstein BN, Kimmel SC, Levin RI, Martiniuk F, Weissmann G (1992) A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. Proc Natl Acad Sci USA 89:9991–9995
125. Guida L, Ohehir RE, Hawrylowicz CM (1994) Synergy between dexamethasone and interleukin-5 for the induction of major histocompatability complex class II expression by human peripheral blood eosinophils. Blood 84:2733–2740
126. Hiromatsu Y, Sato M, Yamada K, Nonaka K. (1991) Inhibitory effects of nicotinamide on recombinant human interferon-γ-induced intercellular adhesion molecule-1 (ICAM-1) and HLA-DR antigen expression on cultured human endothelial cells. Immunol Lett 31:35–39
127. Hiromatsu Y, Sato M, Tanaka K, Ishisaka N, Kamachi J, Nonaka K (1993) Inhibitory effects of nicotinamide on intercellular adhesion molecule-1 expression on cultured human thyroid cells. Immunol 80:330–332
128. Stuhlmeyer KM, Csizmadia V, Cheng G, Winkler H, Bach FH (1994) Selective inhibition of E-selectin, ICAM-1 and VCAM in endothelial cells. Eur J Immunol 24:2186–2190
129. Stolpe A van de, Caldenhoven E, Stade BG, Koenderman L, Raaijmakers JAM, Johnson JP, Saag PT van der (1994) 12-*O*-Tetradecanoylphorbol-13-acetate- and tumor necrosis factor α-mediated induction of intercellular adhesion molecule-1 is inhibited by dexamethasone: functional analysis of the human intercellular adhesion molecule-1 promoter. J Biol Chem 269:6185–6192
130. Bender JR, Sadeghi MM, Watson C, Pfau S, Pardi R (1994) Heterogeneous activation thresholds to cytokines in genetically distinct endothelial cells: evidence for diverse transcriptional responses. Proc Natl Acad Sci USA 91:3994–3998
131. Gerritsen ME, Niedbala MJ, Szczepanski A, Carley WW (1993) Cytokine activation of human macro- and microvessel-derived endothelial cells. Blood Cells 19:325–342
132. Jahnke A, van de Stolpe A, Caldenhoven E, Johnson JP (1995) Constitutive expression of human intercellular adhesion molecule-1 (ICAM-1) is regulated by differentially active enhancing and silencing elements. Eur J Biochem 228:439–446
133. Cornelius LA, Taylor JT, Degitz K, Li LJ, Lawley TJ, Wright Caughman S (1993) A 5′ portion of the ICAM-1 gene confers tissue-specific differential expression levels and cytokine responsiveness. J Invest Dermatol 100:753–758
134. Look DC, Pelletier MR, Holtzman MJ (1994) Selective interaction of a subset of interferon-γ response element-binding proteins with the intercellular adhesion molecule-1 (ICAM-1) gene promoter controls the pattern of expression on epithelial cells. J Biol Chem 269:8952–8958
135. Scheynius A, Engstrand L (1991) Gastric epithelial cells in Helicobacter pylory-associated gastritis express HLA-DR but not ICAM-1. Scand J Immunol 33:237–241
136. Dean NM, McKay R, Condon TP, Bennett CF (1994) Inhibition of protein kinase C-α expression in human A549 cells by antisense oligonucleotides inhibits induction of intercellular adhesion molecule 1 (ICAM-1) mRNA by phorbol esters. J Biol Chem 269:16416–16424
137. Pober JS, Slowik MR, de Luca LG, Ritchie AJ (1993) Elevated cyclic AMP inhibits endothelial cell synthesis and expression of TNF-induced endothelial leukocyte adhesion molecule-1, and vascular cell adhesion molecule-1, but not intercellular adhesion molecule-1. J Immunol 150:5114–5123
138. Renkonen R, Mennander A, Ustinov J, Mattila P (1990) Activation of protein kinase C is crucial in the regulation of ICAM-1 expression on endothelial cells by interferon-γ. Int Immunol 2:719–724
139. Read MA, Neish AS, Luscinskas FW, Palombella VJ, Maniatis T, Collins T (1995) The proteasome pathway is required for cytokine-induced endothelial-leukocyte adhesion molecule expression. Immunity 2:493–506
140. Kurose I, Kubes P, Wolf RE, Anderson DC, Paulson J, Miyasaka M, Granger DN (1993) Inhibition of nitric oxide production: mechanisms of vascular albumin leakage. Circ Res 73:164–171
141. Tiisala S, Majuri M-L, Carpén O, Renkonen R (1994) Genistein enhances the ICAM-mediated adhesion by inducing the expression of ICAM-1 and its counter-receptors. Biochem Biophys Res Commun 203:443–449
142. Abe Y, Gatanaga M, Osuka Y, Kimura S, Burger RA, Granger GA, Gatanaga T (1993) Role of 55- and 75-kDa tumor necrosis factor membrane receptors in the regulation of intercellular adhesion molecules-1 expression by HL-60 human promyelocytic leukemia cells in vitro. J Immunol 150:5070–5079
143. Stade BG, Messer G, Riethmüller G, Johnson JP (1990) Structural characteristics of the 5′ region of the human ICAM-1 gene. Immunobiol 182:79–87
144. Degitz K, Lian-Jie L, Wright Caughman S (1991) Cloning and characterization of the 5′ transcriptional regulatory region of the human intercellular adhesion molecule 1 gene. J Biol Chem 266:14024–14030
145. Wawryk SO, Cockerill PN, Wicks IP, Boyd AW (1991) Isolation and characterization of the promoter region of the human

intercellular adhesion molecule-1 gene. Int Immunol 3:83–93
146. Ballantyne CM, Sligh Jr JE, Dai XY, Beaudet AL (1992) Characterization of the murine ICAM-1 gene. Genomics 14:1076–1080
147. Puch BF, Tjian R (1990) Mechanism of transcriptional activation by Sp1: evidence for coactivators. Cell 61:1187–1197
148. Angel P, Imagawa M, Chiu R, Stein B, Imbra RJ, Rahmsdorf HJ, Jonat C, Herrlich P, Karin M (1987) Phorbol ester-inducible genes contain a common cis element recognized by a TPA-modulated trans-acting factor. Cell 49:729–739
149. Caldenhoven E, Coffer P, Yuan J, van de Stolpe A, Horn F, Kruijer W, van der Saag PT (1994) Stimulation of the human intercellular adhesion molecule-1 promoter by interleukin-6 and interferon-γ involves binding of distinct factors to a palindromic response element. J Biol Chem 269:21146–21154
150. Hou J, Baichwal V, Cao Z (1994) Regulatory elements and transcription factors controlling basal and cytokine-induced expression of the gene encoding intercellar adhesion molecule 1. Proc Natl Acad Sci USA 91:11641–11645
151. Jahnke A, Johnson JP (1994) Synergistic activation of intercellular adhesion molecule 1 (ICAM-1) by TNF-α and IFN-γ is mediated by p65/p50 and p65/c/rel and interferon-responsive factor statlα (p91) that can be activated by both IFN-γ and IFN-α. FEBS Lett 354:220–226
152. Yuan J, Wegenka UM, Lütticken C, Buschmann J, Decker T, Schindler C, Heinrich PC, Horn F (1994) The signalling pathways of interleukin-6 and γ interferon converge by the activation of different transcription factors which bind to common responsive DNA elements. Mol Cell Biol 14:1657–1668
153. Weber C, Calzada-Wack JC, Goretzki M, Pietsch A, Johnson JP, Ziegler-Heitbrock HWL (1995) Retinoic acid inhibits basal and interferon-γ induced expression of intercellular adhesion molecule 1 in monocytic cells. J Leukocyte Biol 57:401–406
154. Resnick N, Collins T, Atkinson W, Bonthron DT, Dewey Jr CF, Gimbrone Jr MA (1993) Platelet-derived growth factor B chain promoter contains a cis-acting fluid shear-stress-responsive element. Proc Natl Acad Sci USA 90:4591–4595
155. Grether-Beck S, Gyufko K, Klammer M, Jahnke A, Johnson JP (1995) Identification of the ultraviolet A1 radiation/singlet oxygen responsive element of the human ICAM-1 gene. Exp Hematol 23:918A
156. Eck SL, Perkins ND, Carr DP, Nabel GJ (1993) Inhibition of phorbol ester-induced cellular adhesion by competitive binding of NF-κB in vivo. Mol Cell Biol 13:6530–6536
157. Ledebur HC, Parks TP (1995) Transcriptional regulation of the intercellular adhesion molecule-1 gene by inflammatory cytokines in human endothelial cells. J Biol Chem 270:933–943
158. Kunsch C, Ruben SM, Rosen CA (1992) Selection of optimal κB/Rel DNA-binding motifs: interaction of both subunits of NF-κB with DNA is required for transcriptional activation. Mol Cell Biol 12:4412–4421
159. Grimm S, Baeuerle PA (1993) The inducible transcription factor NF-κB: structure-function relationship of its protein subunits. Biochem J 290:297–308
160. Parry GCN, Mackman N (1994) A set on inducible genes expressed by activated human monocytic and endothelial cells contain κB-like sites that specifically bind c-Rel-p65 heterodimers. J Biol Chem 269:20823–20825
161. Stein B, Baldwin AS Jr, Ballard DW, Greene WC, Angel P, Herlich P (1993) Cross-coupling of the NF-κB p65 and Fos/Jun transcription factors produces potentiated biological function. EMBO 12:3879–3891
162. Stein B, Cogswell PC, Baldwin AS Jr (1993) Functional and physical associations between NFκB and C/EBP family members. Mol Cel Biol 13:3964–3974
163. Perkins ND, Edwards NL, Duckett CS, Agranoff AB, Schmidt RM, Nabel GJ (1993) A cooperative interaction between NF-κB and Sp1 is required for HIV-1 enhancer activation. EMBO 12:3551–3558
164. Ray A, Prefontaine KE (1994) Physical association and functional antagonism between the p65 subunit of transcription factor NF-κB and the glucocorticoid receptor. Proc Natl Acad Sci USA 91:752–756
165. Caldenhoven E, Liden J, Wissink S, van de Stolpe A, Raaijmakers J, Koenderman L, Okret S, Gustafsson JA, van der Saag PT (1995) Negative cross-talk between RelA and the glucocorticoid receptor: a possible mechanism for the antiinflammatory action of glucocorticoids. Mol Endocrin 9:401–412
166. Scheinman RI, Gualberto A, Jewell CM, Cidlowski JA, Baldwin Jr AS (1995) Characterization of mechanisms involved in transrepression of NF-κB by activated glucocorticoid receptors. Mol Cell Biol 15:943–953
167. Juan TSC, Wilson DR, Wilde MD, Darlington GJ (1993) Participation of the transcription factor C/EBPδ in the acute-phase regulation of the human gene for complement component C3. Proc Natl Acad Sci USA 90:2584–2588
168. Ohh M, Smoith CA, Carpenito C, Takei F (1994) Regulation of intercellular adhesion molecule-1 gene expression involves multiple mRNA stabilisation mechanisms: effects of interferon γ and phorbol myristate acatate. Blood 84:2632–2639
169. Ohh M, Takei F (1994) Interferon-γ and phorbol myristate acetate-responsive elements involved in intercellular adhesion molecule-1 mRNA stabilization. J Biol Chem 269: 30117–30120
170. Zimmerman BJ, Holt JW, Paulson JC, Anderson DC, Miyasaka M, Tamatani T, Todd III RF, Rusche JR, Granger DN (1994) Molecular determinants of lipid mediator-induced leukocyte adherence and emigration in rat mesenteric venules. Am J Physiol 266:H847-H853
171. Arnould T, Michiels C, Remacle J (1993) Increased PMN adherence on endothelial cells after hypoxia: involvement of PAF, CD18/CD11b, and ICAM-1. Am J Physiol 264:C1102-1110
172. Fine JS, Kruisbeek AM (1991) The role of LFA-1/ICAM-1 interactions during murine T lymphocyte development. J Immunol 147:2852–2859
173. Geissler D, Gaggl S, Most J, Greil R, Herold M, Dietrich M (1990) A monoclonal antibody directed against the human intercellular adhesion molecule (ICAM-1) modulates the release of tumor necrosis factor-α, interferon-γ and interleukin 1. Eur J Immunol 20:2591–2596
174. Rothlein R, Kishimoto TK, Mainolfi E (1993) Cross-linking of ICAM-1 induces co-signaling of an oxidative burst from mononuclear leukocytes. J Immunol 152:2488–2495
175. Durieu-Trautmann O, Chaverot N, Cazauban S, Donny Strosberg A, Couraud PO (1994) Intercellular adhesion molecule-1 activation induces tyrosine phosphorylation of the cytoskeleton-associated protein cortactin in brain microvessel endothelial cells. J Biol Chem 269:12536–12540
176. Horssen van M, Loman S, Rijkers GT, Boom SE, Bloem AC (1995) Co-ligation of ICAM-1 (CD54) and membrane IgM negatively affects B cell receptor signaling. Eur J Immunol 25:154–158
177. Arroyo AG, Campanero MR, Sánchez-Mateos P, Zapata JM, Ursa A, del Pozo MA, Sánchez-Madrid F (1994) Induction of tyrosine phosphrylation during ICAM-3 and LFA-1-mediated intercellular adhesion, and its regulation by the CD45 tyrosine phosphatase. J Cell Biol 126:1277–1286
178. Campanero MR, Sánchez-Mateos P, del Pozo MA, Sánchez-Madrid F (1994) ICAM-3 regulates lymphocyte morphology and integrin-mediated T cell interaction with endothelial cell and extracellular matrix ligands. J Cell Biol 127:867–878
179. Juan M, Viñas O, Pino-Otín MR, Places L, Martínez-Cáceres E, Barceló JJ, Miralles A, Vilella R, Fuente MA de la, Vives J, Yagüe J, Gayà A (1994) CD50 (Intercellular adhesion molecule-3) stimulation induces calcium mobilization and tyrosine phosphorylation through $p59^{fyn}$ and $p56^{lck}$ in Jurkat T cell line. J Exp Med 179:1747–1756
180. Fischer H, Gjörloff A, Hedlund G, Hedman H, Lundgren E, Kalland T, Sjögren HO, Dohlsten M (1992) Stimulation of

human naive and memory T helper cells with bacterial superantigen. J Immunol 148:1993–1998
181. Damle NK, Klussman K, Linsley PS, Aruffo A (1992) Differential costimulatory effects of adhesion molecules B7, ICAM-1, LFA-3, and VCAM-1 on resting and antigen-primed CD4+ T lymphocytes. J Immunol 148:1985–1992
182. Altmann DM, Hogg N, Trowsdale J, Wilkinson D (1989) Cotransfection of ICAM-1 and HLA-DR reconstitutes human antigen-presenting cell function in mouse L cells. Nature 338:512–514
183. Maio M, Tessitori G, Pinto A, Temponi M, Colombatti A, Ferrone S (1989) Differential role of distinct determinants of intercellular adhesion molecule-1 in immunologic phenomena. J Immunol 143:181–188
184. Makgoba MW, Sanders ME, Ginther-Luce GE, Dustin ML, Springer TA, Clark EA, Mannoni P, Shaw S (1988) ICAM-1 a ligand for LFA-1-dependent adhesion of B, T and myeloid cells. Nature 331:86–88
185. Vanky F, Wang P, Patarroyo M, Klein E (1990) Expression of the adhesion molecule ICAM-1 and major histocompatibility complex class I antigens on human tumor cells is required for their interaction with autologous lymphocytes in vitro. Cancer Immunol Immunother 31:19–27
186. Jansen JH, van der Harst D, Wientjens GJHM, Kooy-Winkelaar YMC, Brand A, Willemze R, Kluin-Nelemans HC (1992) Induction of CD11a/leukocyte function antigen-1 and CD54/intercellular adhesion molecule-1 on hairy cell leukemia cells is accompanied by enhanced susceptibility to T-cell but not lymphokine-activated killer-cell cytotoxity. Blood 80:478–483
187. Ybarrondo B, O'Rourke AM, Brian AA, Mescher MF (1994) Contribution of lymphocyte function-associated-1/intercellular adhesion molecule-1 binding to the adhesion/signaling cascade of cytotoxic T lymphocyte activation. J Exp Med 179:359–363
188. Dustin ML, Springer TA (1988) Lymphocyte function-associated antigen-1 (LFA-1) interaction with intercellular adhesion molecule-1 (ICAM-1) is one of at least three mechanisms for lymphocyte adhesion to cultured endothelial cells. J Cell Biol 107:321–331
189. Muller WA, Weigl SA, Deng X, Phillips DM (1993) PECAM-1 is required for transendothelial migration of leukocytes. J Exp Med 178:449–460
190. Muller WA (1995) The role of PECAM-1 (CD31) in leukocyte emigration: studies in vitro and in vivo. J Leukoc Biol 57:523–528
191. Chiang MY, Chan H, Zounes MA, Freier SM, Lima WF, Bennett CF (1991) Antisense oligonucleotides inhibit intercellular adhesion molecule-1 expression by two distinct mechanisms. J Biol Chem 266:18162–18171
192. Smith CW, Rothlein R, Hughes BJ, Mariscalco MM, Rudloff HE, Schmalstieg FC, Anderson DC (1988) Recognition of an endothelial determinant for CD18-dependent human neutrophil adherence and transendothelial migration. J Clin Invest 82:1746–1756
193. Oppenheimer-Marks N, Davis LS, Tompkins Bogue D, Ramberg J, Lipsky PE (1991) Differential utilization of ICAM-1 and VCAM-1 during the adhesion and transendothelial migration of human T lymphocytes. J Immunol 147:2913–2921
194. Nawroth PP, Stern DM (1986) Modulation of endothelial cell hemostatic properties by tumor necrosis factor. J Exp Med 163:740–745
195. Fan ST, Brian AA, Lollo BA, Mackman N, Shen NL, Edgington TS (1993) CD11a/CD18 (LFA-1) integrin engagement enhances biosynthesis of early cytokines by activated T cells. Cell Immunol 148:48–59
196. Fan ST, Edgington TS (1993) Integrin regulation of leukocyte inflammatory functions. J Immunol 150:2972–2980
197. Lukacs NW, Strieter RM, Elner VM, Evanoff HL, Burdick MM, Kunkel SL (1994) Intercellular adhesion molecule-1 mediates the expression of monocyte-derived MIP-1α during monocyte-endothelial cell interactions. Blood 83:1174–1178
198. Lord KA, Hoffman-Liebermann B, Liebermann DA (1990) Complexity of the immediate early response of myeloid cells to terminal differentiation and growth arrest includes ICAM-1, Jun-B and histone variants. Oncogene 5:387–396
199. Gordon MY, Clarke D, Atkinson J, Greaves MF (1990) Hemopoietic progenitor cell binding to the stromal microenvironment in vitro. Exp Hematol 18:837–842
200. Avraham H, Cowley S, Chi SY, Jiang S, Groopman JE (1993) Characterization of adhesive interactions between human endothelial cells and megakaryocytes. J Clin Invest 91:2378–2384
201. Kurachi T, Morita I, Murota SI (1993) Involvement of adhesion molecules LFA-1 and ICAM-1 in osteoclast development. Biochim Biophys Acta 1178:259–266
202. Koopman G, Keehnen RMJ, Lindhout E, Newman W, Shimizu Y, van Seventer GA, de Groot C, Pals ST (1994) Adhesion through the LFA-1 (CD11a/CD18)-ICAM-1 (CD54) and the VLA-4 (CD49d)-VCAM-1 (CD106) pathways prevents apoptosis of germinal center B cells. J Immunol 152:3760–3767
203. Fougerolles AR de, Stacker SA, Schwarting R, Springer TA (1991) Characterization of ICAM-2 and evidence for a third counter receptor for LFA-1. J Exp Med 174:253–267
204. Tsukada N, Matsuda M, Miyagi K, Yanagisawa N (1993) Increased levels of intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor receptor in the cerebrospinal fluid of patients with multiple sclerosis. Neurology 43:2679–2682
205. Chihara J, Yamamoto T, Kurachi D, Nakajima S (1994) Soluble ICAM-1 in sputum of patients with bronchial asthma. Lancet 343:1108
206. Rothlein R, Mainolfi EA, Czajkowski, Marlin SD (1991) A form of circulating ICAM-1 in human serum. J Immunol 147:3788–3793
207. Becker JC, Dummer R, Hartmann AA, Burg G, Schmidt RE (1991) Shedding of ICAM-1 from human melanoma cell lines induced by IFN-γ and tumor necrosis factor-α. J Immunol 147:4398–4401
208. Budnik A, Trefzer U, Parlow F, Grewe M, Kapp A, Schöpf E, Krutmann J (1992) Human epidermal keratinocytes are a source of soluble ICAM-1 molecules. Exp Dermatol 1:27–30
209. Leeuwenberg JFM, Smeets EF, Neefjes JJ, Shaffer MA, Cinek T, Jeunhomme TMAA, Ahern TJ, Buurman WA (1992) E-Selectin and intercellular adhesion molecule-1 are released by activated human endothelial cells in vitro. Immunology 77:543–549
210. Pigott R, Dillon LP, Hemingway IH, Gearing AJH (1992) Soluble forms of E-selectin, ICAM-1 and VCAM-1 are present in the supernatants of cytokine activated cultured endothelial cells. Biochem Biophys Res Commun 187:584–589
211. Thomson AW, Satoh S, Nüssler AK, Tamura K, Woo J, Gavaler J, Thiel DH van (1994) Circulating intercellular adhesion molecule-1 (ICAM-1) in autoimmune liver disease and evidence for the production of ICAM-1 by cytokine-stimulated human hepatocytes. Clin Exp Immunol 95:83–90
212. Seth R, Raymond FD, Makgoba MW (1991) Circulating ICAM-1 isoforms: diagnostic prospects for inflammatory and immune disorders. Lancet 338, 83–84
213. Cobb RR, Dubins JS, Warner J, Molony L (1992) Functional expression of soluble ICAM-1 by baculovirus-infected *Sf9* cells. Biochem Biophys Res Commun 185:1022–1033
214. Welder CA, Lee DHS, Takei F (1993) Inhibition of cell adhesion by microspheres coated with recombinant soluble intercellular adhesion molecule-1. J Immunol 150:2203–2210
215. Crump CE, Arruda E, Hayden FG (1993) In vitro inhibitory activity of soluble ICAM-1 for the numbered serotypes of human rhinovirus. Antiviral Chem Chemother 4:323–327
216. Seventer GA van, Shimizu Y, Horgan KJ, Shaw S (1990) The LFA-1 ligand ICAM-1 provides an important costimulatory signal for T cell receptor-mediated activation of resting T cells. J Immunol 144:4579–4586
217. Banks RE, Gearing AJH, Hemingway IK, Norfolk DR, Perren TJ, Selby PJ (1993) Circulating intercellular adhesion

molecule-1 (ICAM-1), E-selectin and vascular cell adhesion molecule-1 (VCAM-1) in human malignancies. Br J Cancer 68:122–124
218. Hvidd L, Theander TG, Elhassan IM, Jensen JB (1993) Increased plasma levels of soluble ICAM-1 and ELAM-1 (E-selectin) during acute plasmodium falciparum malaria. Immunol Letters 36:51–58
219. Clark WM, Coull BM, Briley DP, Mainolfi E, Rothlein R (1993) Circulating intercellular adhesion molecule-1 levels and neutrophil adhesion in stroke. J Neuroimmunol 44:123–126
220. Gearing AJH, Hemingway I, Pigott R, Hughes J, Rees AJ, Cashman SJ (1992) Soluble forms of vascular adhesion molecules, E-selectin, ICAM-1, and VCAM-1: pathological significance. Ann NY Acad Sci 667:324–331
221. Kageshita T, Yoshii A, Kimura T, Kuriya N, Ono T, Tsujisaki M, Imai K, Ferrone S (1993) Clinical relevance of ICAM-1 expression in primary lesions and serum of patients with malignant melanoma. Cancer Res 53:4927–4932
222. Furukawa S, Motohashi T, Matsubara T, Imai K, Okomura K, Yabuta K (1993) Soluble ICAM-1 levels in serum during acute infectious mononucleosis. Scand J Infect Dis 25:249–252
223. Wenisch C, Varijanonta S, Looareesuwan S, Graninger W, Pichler R, Wernsdorfer W (1994) Soluble intercellular adhesion molecule-1 (ICAM-1), endothelial leukocyte adhesion molecule-1 (ELAM-1), and tumor necrosis factor receptor (55kDA TNF-R) on patients with acute *Plasmodium falciparum* malaria. Clin Immunol Immunopathol 71:344–348
224. Zöhrens G, Armbrust T, Pirzer U, Meyer zum Büschenfelde KH, Ramadori G (1993) Intercellular adhesion molecule-1 concentration in sera of patients with acute and chronic liver disease: relationship to disease activity and cirrhosis. Hepatology 18:798–802
225. Shijubo N, Imai K, Shigehara K, Honda Y, Koba H, Tsujisaki M, Hinoda Y, Yachi A, Ohmichi M, Hiraga Y, Abe S (1994) Soluble intercellular adhesion molecule-1 (ICAM-1) in sera and bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis and pulmonary sarcoidosis. Clin Exp Immunol 95:156–161
226. Pforte A, Schiessler A, Gais P, van Kress S, Beer B, Riethmüller G, Ziegler-Heitbrock HWL (1993) Expression of the adhesion molecule ICAM-1 on alveolar macrophages and in serum in extrinsic allergic alveolitis. Respiration 60:221–226
227. Sfikakis PP, Charalambopoulos D, Vayiopoulos G, Oglesby R, Sfikakis P, Tsokos GC (1994) Increased levels of intercellular adhesion molecule-1 in the serum of patients with systemic lupus erythematosus. Clin Exp Rheumatol 12:5–9
228. Tsukada N, Miyagi K, Matsuda M, Yanagisawa N (1993) Increased levels of circulating intercellular adhesion molecule-1 in multiple sclerosis and human T-lymphotropic virus type I-associated myelopathy. Ann Neurol 33:646–649
229. Kobayashi T, Hashimoto S, Imai K, Amemiya E, Yamaguchi M, Yachi A, Horie T (1994) Elevation of serum soluble intercellular adhesion molecule-1 (sICAM-1) and sE-selectin levels in bronchial asthma. Clin Exp Immunol 96:110–115
230. Montefort S, Lai CKW, Kapahi P, Leung J, Lai KN, Chan HS, Haskard DO, Howarth PH, Holgate ST (1994) Circulating adhesion molecules in asthma. Am J Resp Crit Med 149:1149–1152
231. Dalhoff K, Bohnet S, Braun J, Kreft B, Wiessmann KJ (1993) Intercellular adhesion molecule 1 (ICAM-1) in the pathogenesis of mononuclear cell alveolitis in pulmonary sarcoidosis. Thorax 48:1140–1144
232. Riise GC, Larsson S, Lofdahl EG, Andersson BA (1994) Circulating cell adhesion molecules in bronchial lavage and serum in COPD patients with chronic bronchitis. Eur Resp J. 7:1673–1677
233. Williams IR, Kupper TS (1994) Epidermal expression of intercellular adhesion molecule 1 is not a primary inducer of cutaneous inflammation in transgenic mice. Proc Natl Acad Sci USA 91:9710–9714
234. Johnson JP (1991) The role of ICAM-1 in tumor development. Integrins and ICAM-1 in immune responses. Chem Immunol50:143–163
235. Pandolfi F, Trentin L, Boyle LA, Stamenkovic I, Randolph Byers H, Colvin RB, Kurnick JT (1991) Expression of cell adhesion molecules in human melanoma cell lines and their role in cytotoxicity mediated by tumor-infiltrating lymphocytes. Cancer 69:1165–1173
236. Padros MR, Noli MI, Fainboim L (1992) Expression of ICAM-1 (CD54) on normal and leukaemic B cells: implication for the mixed lymphocyte reaction. Clin Exp Immunol 88:329–334
237. Raspadori D, Lauria F, Ventura MA, Rondelli D, Tura S (1993) Expression of adhesion molecules on acute leukemic blast cells and sensitivity to normal LAK activity. Ann Hematol 67:213–216
238. Renkonen R, Paavonen T, Nortamo P, Gahmberg CG (1992) Expression of endothelial adhesion molecules in vivo. Am J Pathol 140:763–767
239. Greve JM, Forte CP, Marlor CW, Meyer AM, Hoover-Litty H, Wunderlich D, McClelland A (1991) Mechanisms of receptor-mediated rhinovirus neutralization defined by two soluble forms of ICAM-1. J Virol 65:6015–6023
240. Johnson JP, Stade BG, Hupke U, Holzmann B, Riethmüller G (1988) The melanoma progression-associated antigen P3.58 is identical to the intercellular adhesion molecule, ICAM-1. Immunobiol 178:275–284
241. Johnson JP, Stade BG, Holzmann B, Schwäble W and Riethmüller G (1989) De novo expression of intercellular-adhesion molecule-1 in melanoma correlates with increased risk of metastasis. Proc Natl Acad Sci USA 86:641–644
242. Giavazzi R, Chirivi RGS, Garofalo A, Rambaldi A, Hemingway I, Pigott R, Gearing AJH (1992) Soluble intercellular adhesion molecule 1 is released by human melanoma cells and is associated with tumor growth in nude mice. Cancer Res 52:2628–2630
243. Altomonte M, Gloghini A, Bertola G, Gasparollo A, Carbone A, Ferrone S, Maio M (1993) Differential expression of cell adhesion molecules CD54/CD11a and CD58/CD2 by human melanoma cells and functional role in their interaction with cytotoxic cells. Cancer Res 53:3343–3348
244. Becker JC, Termeer C, Schmidt RE, Bröcker EB (1993) Soluble intercellular adhesion molecule-1 inhibits MHC-restricted specific T cell/tumor interaction. J Immunol 151:7224–7232
245. Maio M, del Vecchio L (1992) Expression and functional role of CD54/intercellular adhesion molecule-1 (ICAM-1) on human blood cells. Leukemia and Lymphoma 8:23–33
246. Lu D, Thompson JD, Gorski GK, Rice NR, Mayer MG, Yunis JJ (1991) Alterations at the rel locus in human lymphoma. Oncogene 6:1235–1241
247. Neri A, Chang CC, Lombardi L, Salina M, Corradini P, Maiolo AT, Chaganti RSK, Dalla-Favera R (1991) B cell lymphoma-associated chromosomal translocation involves candidate oncogene lyt-10 homologous to NF-κB p50. Cell 67:1075–1087
248. Kerr LD, Duckett CD, Wamsley P, Zhang Q, Chiao P, Nabel G, McKeithan TW, Baeuerle PA, Verma IM (1992) The proto-oncogene BCL-3 encodes an IκB protein. Genes Devel 6:2352–2363
249. Fracchiolla NS, Lombardi L, Salina M, Migliazza A, Baldini L, Berti E, Cro L, Polli E, Maiolo AT, Neri A (1991) Structural alterations of the NF-κB transcription factor lyt-10 in lymphocytic malignancies. Oncogene 8:2839–2845
250. Archimbaud E, Thomas X, Campos L, Magaud JP, Doré JF, Fiere D (1992) Expression of surface adhesion molecules CD54 (ICAM-1) and CD58 (LFA-3) in adult acute leukemia: Relationship with initial characteristics and prognosis. Leukemia 6:265–271
251. Grignani F, Fagioli M, Alkalay M, Longo L, Pandolfi PP, Donti E, Biondi A, Lo Coco F, Grignani F, Pelicci PG (1994) Acute promyelocyte leukemia: from genetics to treatment. Blood 83:10–25

252. Möller P, Henne C, Leithäuser F, Eichelmann A, Schmidt A, Brüderlein S, Dhein J, Krammer PH (1993) Coregulation of the APO-1 antigen with intercullular adhesion molecule-1 (CD54) in tonsillar B cells and coordinate expression in follicular center B cells and in follicular center and mediastinal B-cell lymphomas. Blood 81:2067–2075
253. Takeuchi H, Katayama I (1993) Surface phenotype and adhesion activity of B-cell chronic lymphoid leukemias. Leukemia and lymphoma 10:209–216
254. Kimby E, Rincón J, Patarroyo M, Mellstedt H (1994) Expression of adhesion molecules CD11/CD18 (Leu-CAMs, β2-integrins), CD54 (ICAM-1) and CD58 (LFA-3) in B-chronic lymphocytic leukemia. Leuk Lymphoma 13:297–306
255. Riet I van, Waele M de, Remels L, Lacor P, Schots R, Camp B van (1991) Expression of cytoadhesion molecules (CD56, CD54, CD18 and CD29) by myeloma plasma cells. Br J Hematol 79:421–427
256. Riet I van, Camp B van (1993) The involvement of adhesion molecules in the biology of multiple myeloma. Leukemia and Lymphoma 9:441–452
257. Marotta G, Zagonel V, Pinto A (1993) Induction of LFA-1/CD11a and ICAM-1/CD54 adhesion molecules on neoplastic B cells during in vivo treatment of chronic lymphocytic leukemia with interferon-α_2. Blood 81:267–69
258. Nozawa Y, Yamaguchi Y, Tominaga K, Hojo H, Abe M, Wakasa H (1993) Expression of leukocyte adhesion molecules (ICAM-1/LFA-1) related to clinical behaviour in B cell lymphomas. Hematol Oncol 10:189–194
259. Stauder R, Greil R, Schultz TF, Thaler J, Gattringer C, Radaskiewicz T, Dierich MP, Huber H (1989) Expression of leucocyte function-associated antigen-1 and 7F7-antigen, an adhesion molecule related to intercellular adhesion molecule-1 (ICAM-1) in non-Hodgkin lymphomas and leukaemias; possible influence on growth pattern and leukaemic behaviour. Clin exp Immunol 77:234–238
260. Petrasch S, Kosco M, Schmitz J, Wacker, HH, Brittinger G (1992) Follicular dendritic cells on non-Hodgkin-lymphoma express adhesion molecules complementary to ligands on neoplastic B-cells. Br J Hematol 82:695–700
261. Gregory CD, Murray RJ, Edwards CF, Rickinson AB (1988) Downregulation of cell adhesion molecules LFA-3 and ICAM-1 in Epstein-Barr virus-positive Burkitt's lymphoma underlies tumor cell escape from virus-specific T cell surveillance. J Exper Med 167:1811–1824
262. Rincón J, Prieto J, Patarroyo M (1992) Expression of integrins and other adhesion molecules in Epstein-Barr virus-transformed B lymphoblastoid cells and Burkitt's lymphoma cells. Int J Cancer 51:452–458
263. Billaud M, Calender A, Seigneurin JM, Lenoir GM (1987) LFA-1, LFA-3, and ICAM-1 expression in Burkitt's lymphoma. Lancet:1327–1328
264. Bashir R, Coakham H, Hochberg F (1992) Expression of LFA-1/ICAM-1 in CNS lymphomas: possible mechanism for lymphoma homing into the brain. J Neuro-oncology 12:103–110
265. Pizzolo G, Vinante F, Nadali G, Ricetti MM, Morosato L, Marrocchella R, Vincenzi C, Semenzato G, Chilosi M (1993) ICAM-1 tissue overexpression associated with increased serum levels of its soluble form in Hodgkin's disease. Br J Hematol 84:161–162
266. Fukudome K, Furuse M, Fukuhara N, Orita S, Imai T, Takagi S, Nagira M, Hinuma Y, Yoshie O (1992) Strong induction of ICAM-1 in human T cells transformed by human T-cell-leukemia virus type 1 and depression of ICAM-1 or LFA-1 in adult T-cell-leukemia-derived cell lines. Int J Cancer 52:418–427
267. Leff AR, Hamann KJ, Wegner CD (1991) Inflammation and cell-cell interactions in airway responsiveness. Am J Physiol 260:L189-L206
268. Walker C, Rihs S, Braun RK, Betz S, Bruijnzeel PLB (1993) Increased expression of CD11b and functional changes in eosinophils after migration across endothelial cell monolayers. J Immunol 150:4061–4071
269. Lasalle P, Gosset P, Delneste Y, Tsicopoulos A, Capron A, Joseph M, Tonnell AB (1993) Modulation of adhesion molecule expression on endothelial cells during the late asthmatic reaction: role of macrophage-derived tumor necrosis factor-α. Clin Exp Immunol 94:105–110
270. Lemanske RF Jr, Dick EC, Swenson CA, Vrtis FR, Busse WW (1989) Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. J Clin Invest 83:1–10
271. Wegner CD, Gundel RH, Reilly P, Haynes N, Letts LG, Rothlein R (1990) Intercellular adhesion molecule-1 (ICAM-1) in the pathogenesis of asthma. Science 247:456–459
272. Aoki S, Imai K, Yachi A (1993) Soluble intercellular adhesion molecule-1 (ICAM-1) antigen in patients with rheumatoid arthritis. Scand J Immunol 38:485–490
273. Argenbright LW, Barton RW (1992) Interactions of leukocyte integrins with intercellular adhesion molecule-1 in the production of inflammatory vascular injury in vivo. J Clin Invest 89:259–272
274. Melis M, Gjomarkaj M, Pace E, Malizia G, Spatafora M (1991) Increased expression of leukocyte function associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1) by alveolar macrophages of patients with pulmonary sarcoidosis. Chest 100:910–916
275. Dinther-Janssen AHCM van, van Maarsseveen TCMT, Eckert H, Newman W, Meijer CJLM (1993) Identical expression of ELAM-1, VCAM-1, and ICAM-1 in sarcoidosis and usual interstitial pneumonitis. J Pathol 170:157–164
276. Wuthrich RP, Jevnikar AM, Takei F, Glimcher LH, Kelly VE (1990) Intercellular adhesion molecule-1 (ICAM-1) expression is upregulated in autoimmune murine lupus nephritis. Am J Pathol 136:441–450
277. Kawasaki K, Yaoita E, Yamamoto T, Tamatani T, Miyasaka M, Kihara I (1993) Antibodies against intercellular adhesion molecule-1 and lymphocyte function-associated antigen-1 prevent glomerular injury in rat experimental crescentic glomerulonephritis. J Immunol 150:1074–1083
278. Hill PA, Lan HY, Nikolic-Paterson DJ, Atkins RC (1994) ICAM-1 directs migration and localization of interstitial leukocytes in experimental glomerulonephritis. Kidney Int 45:32–42
279. Chu CM, Liaw YF (1993) Coexpression of intercellular adhesion molecule-1 and class I major histocompatibility complex antigens on hepatocyte membrane in chronic viral hepatitis. J Clin Pathol 46:1004–1008
280. Garcia-Monzon C, Garcia-Buey L, Carcia-Sanchez A, Pajares JM, Moreno-Otero R (1993) Down-regulation of intercellular adhesion molecule 1 on hepatocytes in viral chronic hepatitis treated with interferon α–2b. Gastroenterology 105:462–469
281. Horike N, Onji M, Kumon I, Kanaoka M, Michitaka K, Ohta Y (1993) Intercellular adhesion molecule-1 expression on the hepatocyte membrane of patients with chronic hepatitis B and C. Liver 13:10–14
282. Lim AG, Jazrawi RP, Ahmed HA, Levy JH, Zuin M, Douds AC, Maxwell JD, Northfield TC (1994) Soluble intercellular adhesion molecule-1 in primary biliary cirrhosis: relationship with disease stage, immune activity and cholestasis. Hepatology 20:882–888
283. Mosnier JF, Scoazec JY, Marcellin P, Degott C, Benhamou JP, Feldmann G (1994) Expression of cytokine-dependent immune adhesion molecules by hepatocytes and bile duct cells in chronic hepatitis C. Gastroenterol 107:1457–1468
284. Tipping PG, Hancock WW (1993) Production of tumor necrosis factor and interleukin-1 by macrophages from human atheromateus plaques Am J. Pathol 142:1721–1728
285. Frostegard J, Wu R, Haegerstrand A, Patarroyo M, Lefvert AK, Nilsson J (1993) Mononuclear leukocytes exposed to oxidized low density lipoprotein secrete a factor that stimulates endothelial cells to express adhesion molecules. Atherosclerosis 103:213–219
286. Bini A, Fenoglio Jr JJ, Mesa-Tejada R, Kudryk B, Kaplan KL (1989) Identification and distribution of fibrinogen, fibrin,

and fibrin(ogen) degradation products in atherosclerosis. Arteriosclerosis 9:109–121
287. Poston RN, Haskard DO, Coucher JR, Gall NP, Johnson-Tidey RR (1992) Expression of intercellular adhesion molecule-1 in atherosclerotic plaques. Am J Pathol 140:665–673
288. Wal van der AC, Das PK, Tigges AJ, Becker AE (1992) Adhesion molecules on the endothelium and mononuclear cells in human atherosclerotic lesions. Am J Pathol 141:1427–1433
289. Davies MJ, Gordon JL, Gearing AHJ, Pigott R, Woolf N, Katz D, Kyriakopoulos A (1993) The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM, and E-selection in human atherosclerosis. J Pathol 171:223–229
290. Wood KM, Cadogan MD, Ramshaw AL, Parums DV (1993) The distribution of adhesion molecules in huan atherosclerosis. Histopathology 22:437–444
291. Ross R, (1993) The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 362:801–809
292. Kurose I, Kubes P, Wolf R, Anderson DC, Paulson J, Miyasaka M, Granger DN (1993) Inhibition of nitric oxide production. Circ Res 73:164–171
293. Jerome SN, Doré M, Paulson JC, Smith CW, Korthuis RJ (1994) P-selectin and ICAM-1-dependent adherence reactions: role in the genesis of postischemic no-reflow. Am J Physiol 266:H1316-H1321
294. Shreeniwas R, Koga S, Karakurum M, Pinsky D, Kaiser E, Brett J, Wolitzky BA, Norton C, Plocinski J, Burns DK, Goldstein A, Stern D (1992) Hypoxia-mediated induction of endothelial cell interleukin-1α. J Clin Invest 90:2333–2339
295. Nolte D, Hecht R, Schmid P, Botzlar A, Menger MD, Neumueller C, Sinowatz F, Vestweber D, Messmer K (1994) Role of Mac-1 and ICAM-1 in ischemia-reperfusion injury in a microcirculation model of balb/c mice. Am J Physiol 267:H1320-H1328
296. Deventer SJH van, Büller HR, ten Cate JW, Aarden LA, Hack CE, Sturk A (1990) Experimental endotoxemia in humans: analysis of cytokine release and coagulation, fibrinolytic, and complement pathways. Blood 76:2520–2526
297. Lo SK, Everitt J, Malik AB (1992) Tumor necrosis factor mediates experimental pulmonary edema by ICAM-1 and CD18-dependent mechanisms. J Clin Invest 89:981–988
298. Singer KH, Tuck DT, Sampson HA, Hall RP (1989) Epidermal keratinocytes express the adhesion molecule intercellular adhesion molecule-1 in inflammatory dermatoses. J Invest Dermatol 92:746–750
299. Vejlsgaard GL, Ralfkiaer E, Avnstorp C, Czajkowski M, Marlin SD, Rothlein R (1989) Kinetics and characterization of intercellular adhesion molecule-1 (ICAM-1) expression on keratinocytes in various inflammatory skin lesions and malignant cutaneous lymphomas. J Am Acad Dermatol 20:782–790
300. Sobel RA, Mitchell ME, Fondren G (1990) Intercellular adhesion molecule-1 (ICAM-1) in cellular immune reactions in the human central nervous system. Am J Pathol 136:1309–1316
301. Akiyama H, Kawamata T, Yamada T, Tooyama I, Ishii T, McGeer PL (1993) Expression of intercellular adhesion molecule (ICAM)-1 by a subset of astrocytes in Alzheimer disease and some other degenerative neurological disorders. Acta Neuropathol 85:628–634
302. Zielasek J, Archelos JJ, Toyka KV, Hartung HP (1993) Expression of intercellular adhesion molecule-1 on rat microglial cells. Neurosci Lett 153:136–13
303. Tsukada N, Matsuda M, Miyagi K, Yanagisawa N (1994) In vitro intercellular adhesion molecule-1 expression on brain endothelial cells in multiple sclerosis. J Neuroimmunol 49:181–187
304. Verbeek MM, Otte-Höller I, Westphal JR, Wesseling P, Ruiter DJ, de Waal RMW (1994) Accumulation of intercellular adhesion molecule-1 in senile plaques in brain tissue of patients with Alzheimer's disease. Am J Pathol 144:104–116
305. Washington R, Burton J, Todd III RF, Newman W, Dragovic L, Dore-Duffy P (1994) Expression of immunologically relevant endothelial cell activation antigens on isolated central nervous system microvessels from patients with multiple sclerosis. Ann Neurol 35:89–97
306. Isobe M, Yagita H, Okumura K, Ihara A (1992) Specific acceptance of cardiac allograft after treatment with antibodies to ICAM-1 and LFA-1. Science 255:1125–1126
307. Haug GE, Colvin RB, Delmonico FL, Auchincloss H Jr, Tolkoff-Rubin N, Preffer FI, Rothlein R, Norris S, Scharschmidt L, Cosimi AB (1993) A phase I trial of immunosuppression with anti-ICAM-1 (CD54) mAb in renal allograft recipients. Transplantation 55:766–773
308. Norton J, Sloane JP (1994) A prospective study of cellular and immunologic changes in skin of allogeneic bone marrow recipients. Am J Clin Pathol 101:597–602
309. Bennett CF, Condon TP, Grimm S, Chan H, Chiang MY (1994) Inhibition of endothelial cell adhesion molecule expression with antisense oligonucleotides. J Immunol 152:3530–3540
310. O Roep B, Heidenthal E, de Vries RRP, Kolb H, Martin S (1994) Soluble forms of intercellular adhesion molecule-1 in insulin-dependent diabetes mellitus. Lancet 343:1590–1592
311. Archelos JJ, Mäurer M, Jung S, Toyka K, Hartung HP (1993) Suppression of experimental allergic neuritis by an antibody to the intercellular adhesion molecule ICAM-1. Brain 116:1043–1058
312. Seko Y, Matsuda H, Kato K, Hashimoto Y, Yagita H, Okumura K, Yazaki Y (1993) Expression of intercellular adhesion molecule-1 in murine hearts with acute myocarditis caused by coxsackievirus B3. J Clin Invest 91:1327–1336
313. Fischer A (1991) Anti-LFA-1 antibody as immunosuppressive reagent in transplantation. in: Hogg N (ed) Integrins and ICAM-1 in immune responses. Chem Immunol 50:89–97
314. Balkwill F (1993) Improving on the formula. Nature 361: 206–207
315. Huang YW, Burrows FJ, Vitetta ES (1993) Cytotoxicity of a novel anti-ICAM-1 immunotoxin on human myeloma cell lines. Hybridoma 12:661–675
316. Bloemen PGM, Henricks PAJ, Vanbloois L, van den Tweel MC, Bloem AC, Nijkamp FP, Crommelin DJA, Storm G (1995) Adhesion molecules: a new target for immunoliposome-mediated drug delivery. FEBS Lett 357:140–144
317. Puppo F, Brenci S, Scudeletti M, Lanza L, Bosco O, Indiveri F (1993) Elevated serum levels of circulating intercellular adhesion molecule-1 in HIV infection. AIDS 7:593–594