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Adhesion Receptors Regulate Antigen-Specific Interactions, Localization, and Differentiation in the Immune System

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Antigen-specific killer T cell interactions require cooperation between the T cell receptor for antigen (TcR) and the adhesion molecules on the T cell known as LFA-1, CD2, and CD8 (Springer et al.1987; Martz, 1987; Kishimoto et al.1989; Bierer et al.1989). The high degree of cooperation required between these molecules for successful T cell interactions is illustrated by the ability of monoclonal antibodies (mAb) to each of these structures individually to inhibit T cell mediated killing. All of these molecules are involved in adhesion, and many are also involved in the signalling events attendant upon antigen recognition. Thus, they are most properly referred to as adhesion receptors. The properties of these receptors, and the counter-receptors to which they bind, all of which are glycoproteins, are summarized in Table 1.

TABLE 1: CHARACTERISTICS OF T CELL ADHESION RECEPTORS & COUNTER-RECEPTORS

Receptor	Mass (KDa)	Distribution	Counter-Receptor	Mass (KDa)	Dist.
LFA-1 (CD11a/CD18)	α180,β95	Thymocytes, T&B lymphocytes, LGL monocytes, activated macrophages, neutrophils	ICAM-1 (CD54)	90-110	Restricted, widely inducible by IL-1, TNF, IFN-γ & LPS
			ICAM-2	45	Wide? Constitutive on endothelial cells.
CD2 (LFA-2/T11)	50-58	Thymocytes, T lymphocytes, LGL	LFA-3 (CD58)	55-70	Wide
CD8	30-38,α-α or α-β dimer	Subset of thymocytes & lymphocytes, LGL	MHC Class I	α44,β12	Wide, increased by IFN-α, β, γ
CD4	55	Subset of thymocytes & T lymphocytes, monocytes, macrophages	MHC Class II	α34,β29	Restricted, widely inducible by IFN-γ

References: (Springer et al.1987; Bierer et al.1989; Kishimoto et al.1989)

Although much remains to be learned about how activation regulates lymphocyte interactions in vivo, two distinct molecular adhesion mechanisms recently defined in vitro are likely to be important (Springer et al.1987; Spits et al.1986; Shaw, and Luce, 1987). If CTL lines are maintained in culture in an activated state by weekly stimulation with foreign antigen and addition of T-cell growth factors, they will conjugate with B-lymphoblastoid "target cells" even when the target cells do not express the antigen to which T cells are immune. Such adhesion is not shown by resting T lymphocytes (Dustin, and Springer, 1989). Activation-regulated adhesion is due to binding of the CD2 and LFA-1 molecules on the T cell to LFA-3 and ICAM molecules on the target cell, respectively. As shown by mAb blocking, together these two mechanisms account for all the adhesion; there is little (Spits et al.1986) or no (Springer et al.1987; Shaw, and Luce, 1987) contribution by TcR and the CD4 and CD8 molecules. Although the CD2/LFA-3 and LFA-1/ICAM adhesion mechanisms are required for or greatly contribute to antigen-specific killing, CTL only lyse the target cells if the TcR recognizes specific antigen on the target cell. Thus the TcR is required for triggering. Although TcR (and CD4 or CD8) interaction with peptide-MHC must make a contribution to adhesion, the lack of measurable antigen-specific adhesion by CTL clones suggests that the adhesive contribution by binding to peptide-MHC is at least 10-fold lower than the contribution by CD2 and LFA-1 binding to their counter-receptors.

LFA-1 was first identified based on ability of mAb directed to it to inhibit T cell-mediated killing (Springer et al.1987; Kishimoto et al.1989). It was subsequently found that LFA-1 is required for the adhesion step in CTL-mediated killing, and that it is required for a broad range of leukocyte functions involving adhesion, including T helper and B lymphocyte responses, natural killing, monocyte and granulocyte antibody-dependent cytotoxicity, and adherence to endothelial cells, fibroblasts, and epithelial cells.

A counter-receptor for LFA-1, ICAM-1, was identified using a simple assay called homotypic adhesion, in which homogeneous cell populations such as B or T cell lines adhere to one another to form multicellular clusters (Dustin et al.1988; Springer et al.1987). Although resting lymphocytes do not form homotypic aggregates, they do so when stimulated with phorbol esters; transformed lymphoid cell lines aggregate weakly, or if stimulated, strongly. Homotypic adhesion is completely inhibited by LFA-1 mAb, and is not observed with cell lines established from genetically LFA-1-deficient patients (see below). The ability of $LFA\text{-}1^+$ cells to coaggregate with $LFA\text{-}1^-$ cells in the homotypic adhesion assay showed LFA-1 is not a homophilic receptor which binds to itself, but rather a heterophilic receptor binding to a distinct counter-receptor. A counter-receptor was defined by immunizing mice with $LFA\text{-}1^-$ cells, and selecting mAb which would inhibit LFA-1-dependent homotypic adhesion. This counter-receptor was designated an intercellular adhesion molecule (ICAM-1) (Table 1). Confirming the receptor/counter-receptor relationship, lymphocyte binding to purified ICAM-1 is inhibited with LFA-1 mAb (Kishimoto et al.1989), and purified LFA-1 protein micelles bind to purified ICAM-1 on artificial substrates (Dustin, and Springer, 1989). In contrast to LFA-1 which is an integrin (see below), ICAM-1 is a member of the Ig superfamily with 5 Ig domains (Dustin et al.1988). ICAM-1 is 20% identical to the nervous system adhesion molecules NCAM and myelin associated glycoprotein, which also have 5 Ig-like domains. The binding site for LFA-1 lies within the two, most membrane-distal, Ig

domains of ICAM-1 (D.E. Staunton, M.L. Dustin, T.A. Springer, in preparation).

Induction of ICAM-1 in inflammation is one important means of regulating the LFA-1/ICAM interaction (Dustin et al.1988; Kishimoto et al.1989). In contrast to LFA-1 which is restricted to leukocytes, ICAM-1 has the potential to be expressed on a wide variety of cells. In absence of stimulation, however, ICAM-1 is expressed only on a few cells in a pattern correlating with MHC class II expression (Dustin et al.1986) and which therefore may facilitate antigen-presenting cell interactions. Consistent with its importance in in vitro immune responses (Makgoba et al.1988; Altmann et al.1989), in vivo ICAM-1 is well expressed in lymph node germinal centers both on follicular dendritic cells and on the activated B lymphocytes which congregate in these centers (Dustin et al.1986). Germinal centers are formed in lymph nodes during immune responses to specific antigen and homotypic adhesion involving LFA-1 and ICAM-1 may contribute to their formation. Inflammatory mediators, including lipopolysaccharide, interferon-γ, IL-1, and TNF-α and β cause strong induction of ICAM-1 in a wide variety of tissues (Springer et al.1987; Dustin et al.1988; Kishimoto et al.1989). Expression can reach $>10^6$ sites/cell. Induction of ICAM-1 greatly increases lymphocyte and monocyte binding via their cell surface LFA-1. Plots of lymphocyte binding to purified ICAM-1 reconstituted in planar lipid bilayers are sigmoidal, with no adhesion below a threshold value of 100 ICAM-1 molecules/μm^2. Between 150 and 1,000 ICAM-1 molecules/μm^2, lymphocyte binding rises sharply to a plateau; ICAM-1 expression on unstimulated and maximally stimulated endothelial cells falls below (40 sites/μm^2) and above (1,600/μm^2) these levels, respectively (Dustin, and Springer, 1988). Endothelial, fibroblastic and epithelial cells vary in which cytokines are capable of inducing ICAM-1 expression, and the types of mediators released may therefore help regulate differing patterns of cell localization induced by inflammatory stimuli. Binding of leukocytes to endothelium is the first step in localization of circulating cells at an inflammatory site. In vivo, ICAM-1 induction accompanies T cell-mediated hypersensitivity (allergic) reactions (Wantzin et al.1988), and after administration of γ-IFN and IL-1, its appearance on endothelial cells correlates with sites of mononuclear cell infiltration (Munro et al.1989).

A second LFA-1 ligand differing in tissue distribution from ICAM-1 was originally defined functionally by ability of LFA-1 mAb but not ICAM-1 mAb to inhibit certain cell adhesion assays. Lacking a mAb or any information about the structure of ICAM-2, it was nonetheless cloned based on its functional properties. A cDNA expression library was screened for ability to confer on COS cells the ability to bind to purified LFA-1 coated on Petri dishes. Screening was done in presence of ICAM-1 mAb. An ICAM-2 cDNA clone was isolated which encodes a transmembrane protein which binds to LFA-1 and shares no antigenic determinants with ICAM-1 (Staunton et al.1989). ICAM-2 has 2 Ig-like domains, in contrast to ICAM-1 which has 5, and these are 35% identical to the first 2 domains of ICAM-1. ICAM-1 and ICAM-2 are much more similar to one another than to other members of the Ig superfamily, and thus represent an Ig subfamily specialized to interact with LFA-1. A family of LFA-1 counter-receptors emphasizes the importance of this adhesion mechanism and may be a means of imparting fine specificity and functional diversity. Unlike ICAM-1, ICAM-2 is well expressed basally on endothelial cells and mRNA level is not increased by inflammatory mediators. Whether further ICAM's exist is an open question. The

functional cDNA isolation approach should have wide application for other as yet unidentified adhesion counter-structures.

LFA-1 has noncovalently associated α and β subunits; two other leukocyte, adhesion receptors, Mac-1 and p150,95 have the same β subunit and different α subunits. They function in adhesion of neutrophils and monocytes to other cells and Mac-1 is also a complement receptor specific for iC3b (Kishimoto et al.1989) (Table 2). The important role of these glycoproteins is illustrated in congenital "leukocyte adhesion deficiency" (LAD), in which all 3 $\alpha\beta$ complexes are deficient due to mutation of the common β subunit (Anderson, and Springer, 1987; Kishimoto et al.1989). Patients have recurring infections which are often fatal in childhood unless corrected by bone marrow transplantation. Patient monocytes and neutrophils are unable to bind to and cross the endothelium at sites of infection, leading to a lack of pus formation. Chemoattractants both increase surface expression of Mac-1, and make it qualitatively more active (Anderson, and Springer, 1987; Kishimoto et al.1989; Wright, and Meyer, 1986; Buyon et al.1988; Lo et al.1989). β subunit mAb administration in vivo mimics defects in LAD, and appears clinically useful in inhibiting leukocyte extravasation and neutrophil-mediated tissue injury in myocardial infarction and ischemic shock (Kishimoto et al.1989).

Sequencing of the β subunit common to LFA-1, Mac-1, and p150,95 revealed 45% identity to a subunit of a chicken receptor for fibronectin, and conservation of all 56 cysteine residues (Kishimoto et al.1989). This provided evidence for the existence of a family of receptors which mediate both cell-cell and cell-matrix interactions, and which are now called the integrins (Hynes, 1987). Sharing of a common β subunit by LFA-1, Mac-1, and p150,95, which may also be called the leukocyte integrins, or β2 (CD18) subfamily, also provided a model for understanding the subunit relationships of 2 other integrin subfamilies which share the distinctive β1 (CD29) and β3 (CD61) integrin subunits (Table 2).

Each integrin contains a single noncovalently associated α subunit of ~130-180 kD and β subunit of ~90-110 kD. The α subunits are 25-65% identical in amino acid sequence and the β subunits are 37-45% identical; the structural and functional similarities are so strong that integrins should be considered a protein family rather than a superfamily (Kishimoto et al.1989). The association of multiple α subunits with the same β subunit generates distinctive ligand specificities. Although there is no promiscuity among β1, β2, and β3 in interacting with one another's α subunits, recently 2 β subunits designated β4 and β5 have been found to associate with α6 and αv subunits alternatively to β1 and β3, respectively (Kajiji et al.1989; Cheresh et al.1989). This also alters ligand specificity, suggesting both α and β subunits interact with ligand, which has been confirmed by crosslinking to small ligand peptides (D'Souza et al.1988).

A number of β1 subfamily members are expressed on leukocytes of different stages of differentiation; the designation VLA (very late activation) denotes the appearance of VLA-1 and VLA-2 on lymphocytes 2-4 weeks after antigen stimulation in vitro (Hemler, 1988). However, VLA is not an apt acronym because some VLA molecules are basally expressed on leukocytes, and expression on nonhematopoietic cells does not require activation (Table 2). The ligands recognized by β1 integrins (Table 2) show interesting patterns of expression in the extracellular matrices,

TABLE 2. THE INTEGRIN FAMILY OF CELL-CELL AND CELL-MATRIX RECEPTORS

SUBUNITS, NAMES		LIGANDS[a]	RGD ROLE	DISTRIBUTION NON-LEUK[b]	LEUK[c]
$\alpha 1\beta 1$	CD-/CD29,VLA-1	LM,CO	-	F,BM	B*,T*
$\alpha 2\beta 1$	CD49b/CD29,VLA-2	CO	-	P,F,EN,EP	T*
$\alpha 3\beta 1$	CD-/CD29,VLA-3	FN,LM,CO	-	EP,F	
$\alpha 4\beta 1$	CD49d/CD29,VLA-4	FN	-	NC,F	B,T,M,LGL
$\alpha 5\beta 1$	CD-/CD29,VLA-5,FNR	FN	+	F,EP,EN,P	Th,T*
$\alpha 6\beta 1$	CD49f/CD29,VLA-6	LM	-	P	
$\alpha 6\beta 4$	CD49f/CD-,αEb4	LM	-	E	
$\alpha L\beta 2$	CD11a/CD18,LFA-1	ICAM-1,2	-		B,T,M,G
$\alpha M\beta 2$	CD11b/CD18,Mac-1,CR3	C3bi,FX?,FB?	?		M,G
$\alpha X\beta 2$	CD11c/CD18,p150,95	?	?		M,G
$\alpha IIb\beta 3$	CD41/CD61,gpIIb,IIIa	FB,FN,vWF,FB	+	P	
$\alpha V\beta 3$	CD51/CD61,VNR	VN,FB,vWF,TSP	+	EN	
$\alpha V\beta 5$	CD51/CD-	VN,FN	+	C	

a. LM, laminin; CO, collagen; FN, fibronectin, FB, fibrinogen; FX, Factor X; VN, vitronectin; vWF, von Willebrand factor; TS, thrombospondin.
b. EN, endothelial cells; EP, epithelial cells; F, fibroblasts; NC, crest, melanocytes; P, platelets; C, carcinomas; BM, basement membrane associated.
c. B, B lymphocytes; T, T lymphocytes; *, activated lymphocytes only; Th, thymocytes; M, monocytes; G, granulocytes; LGL, large granular lymphocytes.

References: (Kishimoto et al.1989; Hynes, 1987; Ruoslahti, and Pierschbacher, 1987; Hemler, 1988; Kunicki et al.1988)(Wayner et al.1988; Takada, and Hemler, 1989; Holzmann et al.1989; Takada et al.1989; Sonnenberg et al.1988; Kajiji et al.1989; Plow, and Ginsberg, 1989; Cheresh et al.1989)

basement membranes, and lamina of different tissues (Ruoslahti, and Pierschbacher, 1987). Induction of VLA-1, 2, 3, and 5 expression during leukocyte activation may be of great importance in controlling localization of lymphocytes and monocytes in inflammation. In contrast, VLA-4 (CD49d/CD29) is present on resting as well as activated lymphocytes (Hemler, 1988), is a fibronectin receptor (E. Wayner, unpublished), a Peyer's patch homing receptor (Holzmann et al.1989), participates in T cell-mediated killing (Takada et al.1989), and can mediate lymphocyte homotypic adhesion stimulated by certain VLA-4 mAb (B.W. McIntyre, unpublished). There may be some functional redundancy among VLA-4 and LFA-1. A role for VLA-5 in T lymphocyte activation suggests the importance of the extracellular matrix in regulating immune responses (Matsuyama et al.1989).

All integrin α subunits have 3-4 tandem repeats of a putative divalent cation binding site motif, and require Ca^{2+}, Mg^{2+}, or Mn^{2+} for function (Kishimoto et al.1989). LFA-1 α has 3 such repeats and has been shown to bind Mg^{2+}, correlating with the requirement for Mg^{2+} in T cell adhesion and in binding of purified LFA-1 to purified ICAM-1 (Dustin, and Springer, 1989). All 3 leukocyte integrin α subunits, and one of the VLA α subunits, have a domain of 200 amino acids not present in other integrin α subunits, and hence termed the "inserted" or I domain.

The I domains are homologous to ligand binding repeats in von Willebrand factor and other proteins, and may confer modes of ligand recognition in addition to those shared by all integrins (Kishimoto et al.1989).

The amino acid sequence arginine-glycine-aspartic acid (RGD in the one letter code) is a key motif recognized by 4 different integrins within at least 6 different ligands (Ruoslahti, and Pierschbacher, 1986; Ruoslahti, and Pierschbacher, 1987) (Table 2). Short peptides containing this sequence inhibit binding to this sequence within ligands as well as to related sequences within fibrinogen, but do not affect LFA-1 binding to ICAM's (Kishimoto et al.1989); Mac-1 binding to C3bi and fibrinogen however involves RGD-like sequences (Wright et al.1988).

As discussed above, one mechanism for regulating the LFA-1/ICAM-1 interaction is by changing the surface density of ICAM-1 after cytokine stimulation. In vitro or in vivo, increased expression of ICAM-1 is first seen after 4-6 h and is maximal by 9-24 h (Dustin et al.1988; Munro et al.1989; Kishimoto et al.1989). This is typical of regulation at the mRNA level of surface adhesion receptor density, and appears true for CD2 and LFA-3 as well. Alteration of cell surface charge, another mechanism for regulating cell interactions, involves a change in glycoprotein sialylation; replacement of cell surface sialic acid requires de novo glycoprotein biosynthesis (Reichner et al.1988) and glycoprotein turnover, which is on the order of 12-24 h. However, T cells can regulate adhesion over a much shorter time scale, adhering to target cells, delivering a lethal hit, deadhering, and engaging in repeated target cell interactions, with a cycle time as short as 15-30 min (Martz, 1977). What mechanism is involved? Data on CTL primed in vivo, show that in contrast to in vitro stimulated cells, they can adhere in an antigen-specific manner (Martz, 1987). This would only be compatible with the importance of adhesion receptors in cell interactions if their activity was stimulated by the TcR (Martz, 1987; Springer et al.1987; Rothlein, and Springer, 1986). A second mechanism for regulating the LFA-1/ICAM-1 interaction, which is stimulated by the TcR and changes the avidity of LFA-1 over a timescale of minutes has now been defined (Dustin, and Springer, 1989).

Using cells coexpressing LFA-1 and ICAM's, and testing binding to plastic substrates coated with either purified ICAM-1 or purified LFA-1, regulation of the avidity of cellular LFA-1 and of cellular ICAM-1 can be separately tested (Dustin, and Springer, 1989). Stimulation of resting T lymphocytes with TcR crosslinking with mAb converts cellular LFA-1 from a low to high avidity state, whereas cellular ICAM-1 is constitutively avid. There is no change in LFA-1 surface density. In contrast to T cell clones, resting peripheral blood T lymphocytes do not conjugate with B lymphocyte target cells. However, TcR stimulation induces conjugate formation due to an increase in LFA-1 avidity; there is little or no increase in CD2 avidity. The high avidity state peaks 5-10 min after TcR stimulation and returns to the low avidity state by 30 min; kinetics are influenced by the amount of TcR crosslinking. Subsequent addition of phorbol ester returns LFA-1 to the high avidity state, demonstrating the adhesion machinery is still intact. In contrast to TcR stimulation, after phorbol ester stimulation LFA-1 does not return to the low avidity state. Inhibition by dibutryl cAMP of stimulation via the TcR, and stimulation by phorbol esters which act on protein kinase C, strongly suggest that the TcR and LFA-1 are linked by intracellular signalling pathways.

Based on these findings the following model can be proposed for cooperation between the TcR and adhesion molecules to mediate antigen specific recognition (Dustin, and Springer, 1989). On contact with cells bearing specific antigen, TcR ligation generates intracellular signals which lead to energy-dependent conversion of LFA-1 to a high avidity state, favoring LFA-1/ICAM dependent adhesion. Antigen specificity is maintained because the input of energy to convert LFA-1 to the high avidity state, whether this energy is used to fuel protein phosphorylation, LFA-1 redistribution, or some other mechanism, is controlled by the TCR. Cellular energy expended in converting LFA-1 to a high avidity state helps drives the adherence/nonadherence equilibrium toward stable adherence, and is analogous to the use of ATP to favor an otherwise energetically unfavorable reaction in intermediary metabolism. Since TcR binding to peptide MHC does not have to stabilize cell-cell adhesion but instead triggers adhesion amplification, this provides a mechanism for greatly increasing the sensitivity of T cells by lowering the number of TcR-ligand interactions required for antigen recognition. This view of adhesion strengthening is consistent with the recent observation in murine T cell clones that LFA-1 and talin, a cytoskeletal protein which co-localizes with a number of integrins at sites of adhesion, redistribute to sites of interaction with antigen bearing B cells, but not antigen-negative B cells (Kupfer, and Singer, 1989). It is intriguing that redistribution of LFA-1 and talin has been shown to be highly sensitive to low antigen concentrations and may correlate with the high avidity state of LFA-1.

The transience of TcR-stimulated increase in LFA-1 avidity provides a mechanism for regulating the adhesion/deadhesion cycle (Dustin, and Springer, 1989). It is proposed that the TcR triggers a cascade of phosphorylation events or second messengers such that early events lead to an increase in LFA-1 avidity, while later events are responsible for lowering LFA-1 avidity. The kinetics of LFA-1 avidity changes measured after TcR activation by mAb crosslinking are in good agreement with those previously measured for CTL contacting antigen-bearing target cells. Highly active CTL bind to targets rapidly (0.2-2 min.) and can deliver the lethal hit and disengage from the target within an additional 6 min (Martz, 1977; Poenie et al.1987). Antigen density and hence the number of TcR engaged may influence the kinetics of the signalling cascade and thus the kinetics of avidity regulation. Duration of adhesion may also be influenced by the level of ICAM expression and whether ICAM-1 or ICAM-2 is the ligand. It is important to remember that since ICAM-1 is inducible by cytokines (Springer et al.1987; Dustin et al.1988), T cell stimulation could lead to induction of ICAM-1 on antigen presenting cells, and secondarily alter the kinetics of T cell interactions.

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