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Intercellular Adhesion Molecule 1 (ICAM-1): Getting a Grip on Leukocyte Adhesion

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To mediate their immune effector functions leukocytes travel and continuously sample different cellular environments. They must be able to stop, process stimulatory signals from transient cell contacts, and move on. Their recruitment to sites of inflammation involves a sequence of rolling along capillary vessel walls, followed by chemokine-induced arrest and migration across a tight layer of vascular endothelial cells (1, 2). Leukocyte adhesion and detachment from other cells must be highly regulated processes. The main challenge early on in the field was to identify the receptor–ligand interactions involved in this complex process and to understand how they regulated lymphocyte function and antigen recognition. The discovery of ICAM-1 (CD54) as a ligand of the β_2 integrin lymphocyte function-associated antigen (LFA)-1 ($\alpha_L\beta_2$ or CD11a-CD18) established the receptor–ligand pair of a key adhesion pathway, and revealed upregulation of ligand expression by inflammatory cytokines as an important switch to initiate adhesion (3, 4).

The β_2 integrin lymphocyte function-associated antigen (LFA)-1 ($\alpha_L\beta_2$ or CD11a-CD18) was identified through a mAb screen for inhibition of target cell lysis by cytotoxic T lymphocytes (CTL). To focus the search on molecules expressed by the effector cell and not the target, rats were immunized with mouse CTL, and mouse CTL were tested in a xenogeneic mouse CTL anti-rat target cell system in the presence of rat mAbs. This led to the identification of lymphocyte function-associated antigen (LFA)-1 in 1981, and demonstration of its role at the early step of CTL–target cell conjugate formation (5, 6). Other screens identified LFA-2 (CD2) and LFA-3 (CD58) as molecules associated with CTL activity (7). It then took several years to sort out adhesion pathways, establish combinations of receptor–ligand pairs, and finally identify ICAM-1 as a ligand for LFA-1, as reported in 1986 (3, 4).

In 1982, Timothy Springer proposed two hypotheses to account for the contribution of LFA-1 to the specific recognition of target cells by T cells (8). One was that LFA-1 and CD8 controlled distinct steps in a sequential pathway leading to antigen-receptor specific recognition and target cell lysis. The second hypothesis, eminently prescient, proposed that a large complex consisting of an as-of-yet unknown antigen receptor bound to MHC, of CD8 contacting both the receptor and the MHC, and of LFA-1 binding to a ligand on the target cell. LFA-1 would not contribute to specificity but would instead strengthen adhesion or regulate adhesion directly, to increase the range of avidities that can promote antigen recognition.

Two important studies set the stage for the identification of an LFA-1 ligand. First, Stephen Shaw used CTL clones and mAb-mediated inhibition of conjugate formation and of target

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cell lysis to show that adhesion mediated by CD2 and LFA-3 had similar properties, suggesting that they belonged to one adhesion pathway, while adhesion through LFA-1 was a distinct pathway, as it required divalent cations and was temperature-dependent (9). These results strongly suggested that CD2 and LFA-3 formed one ligand–receptor pair, a fact indeed established a year later (10), and that a ligand for LFA-1 was still a missing piece. At the same time, Rothlein and Springer were further investigating the properties of LFA-1 and showed that lymphocytes underwent LFA-1-dependent self aggregation when stimulated with phorbol ester, an activator of protein kinase C (11). Phorbol ester was not acting at the level of LFA-1 expression. A key finding was that lymphocytes from LFA-1-deficient patients (12) failed to self aggregate but could still form LFA-1-dependent conjugates with lymphocytes from normal donors, implying that LFA-1 was not promoting adhesion through homophilic interaction and that a ligand for LFA-1 was expressed on the LFA-1-deficient lymphocytes.

With this information at hand, Rothlein et al. devised a screening strategy to isolate mAbs specific for LFA-1 ligands (3). They immunized mice with an LFA-1-deficient human B cell line and screened hybridomas for inhibition in their simple phorbol ester-induced aggregation assay with LFA-1^+ human lymphocytes. As aggregation was not blocked by anti-CD2 and anti-LFA-3 Abs, the screen was designed to identify novel molecules distinct from CD2 and LFA-3. Out of 600 hybridomas, one (RR1/1) inhibited lymphocyte aggregation almost as well as mAbs to LFA-1. The molecule identified by RR1/1 was biochemically distinct from LFA-1, and called intercellular adhesion molecule 1 (ICAM-1). In addition, a T lymphocyte cell line that expressed very little ICAM-1 was positive for a phorbol ester-induced LFA-1-dependent aggregation that was insensitive to inhibition by RR1/1, suggesting the existence of other ligands. Other members of the ICAM family have since been identified. ICAM-2 and ICAM-3 are expressed primarily on leukocytes, ICAM-4 on erythrocytes, and ICAM-5 in the brain (13, 14).

A detailed characterization of ICAM-1 by Dustin et al. was published at about the same time, the most interesting property being a strong upregulation of ICAM-1 expression by IL-1 and interferon (IFN)-γ (4). A low basal level of ICAM-1 expression level was upregulated transcriptionally by IL-1 and interferon (IFN)-γ. They showed by flow cytometry and immunohistochemistry that ICAM-1 was widely expressed on different cell types, including tissue macrophages and dendritic cells. It was also expressed on non-hematopoietic cells such as vascular endothelial cells, thymic and mucosal epithelial cells, and dermal fibroblasts. While ICAM-1 on lymphoid cells was required for phorbol ester-induced aggregation it was not required for lymphocyte binding to ICAM-1^+ fibroblasts. Strong staining for ICAM-1 on vascular endothelial cells in T cell areas suggested a role in lymphocyte migration towards inflammatory sites. The paper included a figure of a combined visible and fluorescence microscopy image showing tight contacts formed by activated leukocytes, which spread out on human dermal fibroblasts, certainly a prelude to many striking images produced by Dustin and his colleagues over the years.

From these two landmark papers, the Springer group proposed that ICAM-1 was a ligand for LFA-1. This point was nailed a year later by direct binding of LFA-1^+ cells to purified ICAM-1 inserted into artificial lipid membranes (15). Shaw's group further established that B, T, and myeloid cells bound to purified ICAM-1, with properties similar to LFA-1-dependent adhesion to target cells (16). The primary structure of ICAM-1 was deduced from the sequence of cDNA clones isolated either by expression cloning (17) or by designing synthetic oligonucleotides based on ICAM-1 peptide sequence information (18). It was quite a surprise to find that ICAM-1 was made up of Ig-like domains and lacked the RGD motif (arginine-glycine-aspartic acid) found in other ligands of the integrin family.

The implication of an LFA-1-dependent adhesion stimulated by phorbol ester, as reported in 1986 (11), was not lost on the authors, who stated: “The present findings…raise an interesting question. Does binding of an effector cell to a target cell bearing specific antigen stimulate the effector cell, leading to increased LFA-l-dependent adherence? If so, specific receptor-ligand interactions themselves need not contribute all the binding energy required for the cell interaction, but would trigger an LFA-l-dependent mechanism for amplifying the binding energy. Thus, adhesion could be accomplished with a fewer number of receptor-antigen interactions and specific antigen recognition would be more sensitive.” This foresighted prediction was proven correct when Dustin and Springer reported in 1989 that LFA-l-dependent binding to ICAM-1 was dependent on “inside-out” signaling by the T cell antigen receptor (19). Chemokine receptors on T cells can also transmit inside-out signaling. Chemokines bound to endothelium induce a transient extended conformation of LFA-1, thereby providing a tight spatial and temporal regulation of binding to ICAM-1 (20). Thus, the T cell response to ICAM-1 is highly regulated.

Subsequent studies, including the elucidation of high resolution structures of several integrins, have revealed a complex regulation at many levels, with important roles of conformational changes and attachment to the cytoskeleton. Structural and functional analyses of integrin–ligand interactions have also demonstrated a role for force in integrin binding and signaling, a process referred to as mechanotransduction (21-23). ICAM-1 is attached to the actin cytoskeleton through α-actinin (24) or ezrin (25), and such tethering of ICAM-1 is required for LFA-1-dependent NK cell stimulation (26). The induction of stable integrin-dependent adhesiveness in T cells by chemokines requires the application of shear forces (27).

ICAM-1 serves as receptor for rhinovirus, the major causative agent of the common cold virus (28, 29), and is one of the several receptors used by *Plasmodium falciparum* to promote binding of infected erythrocytes to vascular endothelium (30, 31). These pathogens have exploited binding to ICAM-1 for their own purpose and stand to benefit from the ICAM-1 upregulation that is caused by the immune response they trigger.

It would have been hard to envision many years ago, when strong binding by leukocytes to any type of cell would have been considered an impediment to their role as patrollers of the immune system, that tight adhesion to ICAM-1 could be so essential (32) and finely regulated. The insights and feats of a few pioneers have irreversibly changed this view.

Acknowledgments

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Abbreviations used

CTL	cytotoxic T lymphocyte
ICAM	intercellular adhesion molecule
IFN	interferon
LFA	leukocyte function-associated antigen