# The CD2–LFA-3 and LFA-1–ICAM pathways: relevance to T-cell recognition

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*No process is more central to T-lymphocyte function than cell–cell adhesion, yet it is only recently that interest in lymphocyte adhesion has burgeoned. Neglect of adhesion is particularly surprising since immunologists are surrounded by a veritable sea of adhesive interactions of lymphocytic cells: transformed lymphocytes grow in aggregates, stimulated lymphocytes aggregate and T cells conjugate with their targets. In retrospect, it is obvious that all lymphocyte adhesion (both antigen-specific and seemingly non-specific adhesive interactions) has to be based on specific receptor–ligand interactions. In this review Malegapuru Makgoba, Martin Sanders and Stephen Shaw focus primarily on the two molecular pathways of lymphocyte adhesion that have been shown to play a critical role in facilitation of antigen-specific recognition, namely CD2 and its ligand, lymphocyte function associated antigen-3 (LFA-3), and LFA-1 and its ligand, intercellular adhesion molecule-1 (ICAM-1). A variety of excellent recent reviews have dealt with this and related aspects of T-cell adhesion[1–12]. Of particular interest is the review that follows in this issue: it deals with the CD44 molecule which has also been implicated in both adhesion and activation of T cells[11].*

The two molecular pathways described in this review are part of an ensemble of molecules implicated in T cell adhesion (Fig. 1). In addition to those illustrated, other molecules present on activated, but not resting, T cells have been implicated in T-cell adhesion [e.g. p150,95 (CD11c)] or are candidates to do so [e.g. VLA-1 (CD49a)].

It is helpful to classify these adhesion molecules into subgroups according to various criteria, even though such classifications generally require oversimplifications. The first critical distinction is between molecules directly involved in effecting adhesion through receptor–ligand interaction and those that are involved in regulating adhesion. The LFA-1–ICAM-1 and CD2–LFA-3 molecules are the only pairs that have been definitively implicated as receptor–ligand pairs by demonstration that they mediate adhesion when biochemically purified[2,3,6,13–16]. In contrast, other molecules like the T-cell receptor (TCR)[17], CD44 (Ref. 11) and E2 may be involved as regulators of adhesion; such regulation will undoubtedly prove critical (see below).

A second distinction is between molecules that are primarily involved in adhesion and those primarily involved in signal transduction. This distinction has become blurred by recent observations that many so-called adhesion molecules also function in signal transduction[2,3].

A third distinction is between molecules that are thought to contribute a major fraction of the total adhesive bond strength, and those that contribute little to that strength. The CD2 and LFA-1 pathways appear to be the major contributors in model systems such as T-cell adhesion to lymphoid cells[18]; other molecules, such as CD4, can mediate adhesion when over-expressed *in vitro* but appear to be minor contributors under physiological conditions.

A fourth means of categorizing these molecules is to distinguish between molecules involved in 'homing' (antigen-*non*specific process of preferential migration of T cells to a site) versus 'recognition-facilitation' (facilitation of the process of antigen-*specific* recognition and subsequent adhesion-dependent events). CD2–LFA-3 and LFA-1–ICAM-1 would generally be viewed as 'recognition-facilitation' molecules and VLA-4, MEL-14, and CD44 (Ref. 11) viewed as 'homing' molecules; however, this distinction also becomes blurred since VLA-4 can contribute to antigen-specific recognition[19], and LFA-1 can contribute to homing[20,21].

## Characteristics of the adhesion molecules

Table 1 summarizes some of the important features of the CD2–LFA-3 and LFA-1–ICAM pathways of adhesion, and the molecules involved. For convenience we shall use the term 'receptor' to refer to the structures CD2 and LFA-1 on the T cell and the term 'ligand' for the apposing structure.

Of the five receptors/ligands under discussion, all but one constitute part of the immunoglobulin supergene family based on their sequence. LFA-1, the exception, is a member of a distinct, large and functionally important family of adhesion molecules known as the integrins[22–24]. LFA-1, like all members of this extended family, is a heterodimer of two non-covalently associated transmembrane proteins; LFA-1 has a unique $\alpha$ chain (CD11a) and a $\beta$ chain (CD18) which also constitutes part of the related molecules MAC-1 (CD11b) and p150,95 (CD11c). Both the CD18 and CD11a chains are homologous to the chains of other integrins and share their distinctive features such as binding sites for divalent cations. The most provocative difference is the inclusion in the CD11a, CD11b and CD11c chains of an 'inserted (I)-domain' of about 200 amino acids near the amino terminus which has sequences homologous to repeats in von Willebrand factor, chicken cartilage matrix protein and a region of complement factor B (Ref. 22). Sites in this I-domain might function as binding sites in cell–cell

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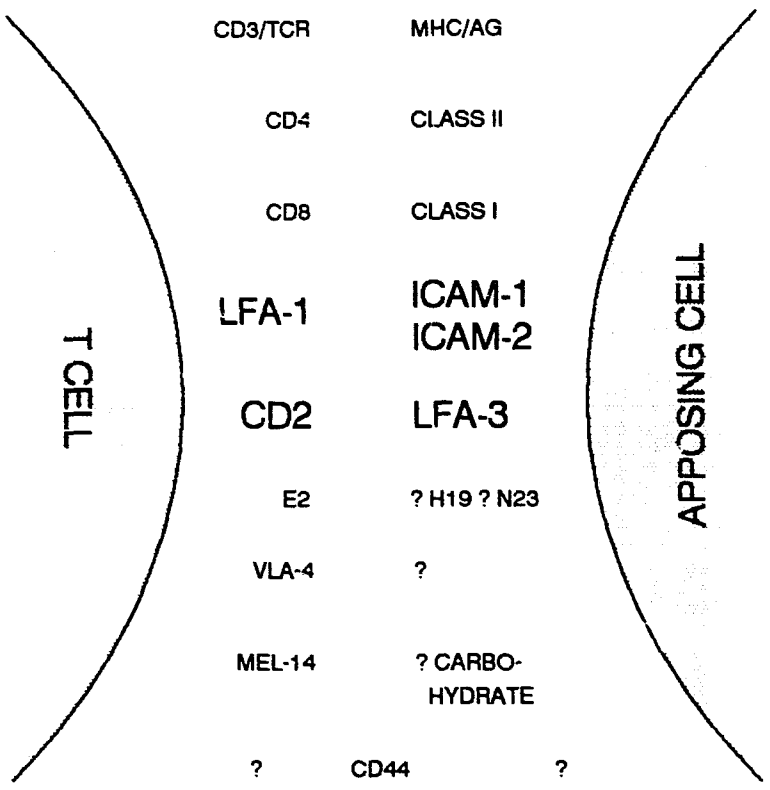


**Fig. 1.** *Examples of molecules present on resting T cells which have been implicated in T-cell adhesion. Nomenclature variations include LFA-1 (CD11a/CD18), CD2 (LFA-2, T11), E2 (MIC2), VLA-4 (CD49d), CD44 (Hermes, Pgp-1, ECMRIII), ICAM-1 (CD54), LFA-3 (CD58), H19 (N4). CD44 is shown between cells rather than on either cell because it has been implicated in adhesion on both sides and in activation on the T-cell side.*

adhesion. The LFA-1 molecule is widely expressed by cells of hematopoietic origin and is used in a variety of lymphocyte, monocyte, natural killer and granulocyte interactions with other cells[1,4].

ICAM-1 (CD54) was first inferred to be a ligand for LFA-1 on the basis of monoclonal antibody (mAb) inhibition of LFA-1-dependent adhesion, and soon thereafter was proven to be a ligand by studies with purified protein[15,16,25,26]. ICAM-1 is an integral membrane glycoprotein with five immunoglobulin-like domains[27,28], and particularly strong homology to two Ig superfamily proteins implicated in neural cell adhesion: myelin-associated glycoprotein (MAG) and neural cell adhesion molecule (NCAM). The receptor–ligand interaction between the integrin LFA-1 and the Ig-like ICAM-1 is an interesting and unprecedented interaction between these two families of surface molecules, particularly so because ICAM-1 lacks the RGD tripeptide site found on other integrin ligands. The possibility that carbohydrate may play an important role in ICAM-1 function is highlighted by the seven potential *N*-linked glycosylation sites, its extensive glycosylation (generally at least 20 kDa), and the variation in its glycosylation between different cell types.

Because it is an important ligand for LFA-1, ICAM-1 is fundamental to many immunologic reactions including antigen-specific T-cell recognition and lysis of certain target cells[25,26,29]. Interesting aspects of its regulation are discussed below. More recently, a number of unexpected features of ICAM-1 have been revealed. ICAM-1 has been shown to be the receptor for the major group of human rhinoviruses[30,31] – the cause of the common cold! It is also associated with the 55 kDa CD25 chain of the interleukin 2 (IL-2) receptor (Ref. 32 and T.A. Waldmann, unpublished) and is identical to a melanoma-associated antigen[33–35].

Multiple functional approaches suggested that ICAM-1 is not the only ligand for LFA-1 (Refs 25, 26, 29). This inference has been confirmed by the cloning and transfection of a gene ICAM-2, whose product also serves as a ligand for LFA-1 (Ref. 36). Its two Ig-like domains are homologous to the distal two domains of ICAM-1, but its expression and regulation are quite different (see below). Further studies await the isolation of a monoclonal antibody specific for ICAM-2. It also remains to be determined whether there will be other ligands for LFA-1.

By comparison to the LFA-1–ICAM interactions, the CD2–LFA-3 interaction appears quite simple: a one-chain receptor interacting with a unique one-chain ligand. There is also the suggestion of evolutionary simplicity in that the genes encoding the CD2 and LFA-3 molecules are in proximity to each other on chromosome 1 and the molecules are both part of the Ig supergene family with particular homologies to each other[37–39]. Finally, their patterns of expression are relatively simple. The virtual restriction of CD2 expression to T cells and the almost ubiquitous distribution of LFA-3 is consistent with the view that this pathway facilitates T-cell adhesion to any cell type requiring surveillance.

However, the simplicity of the CD2–LFA-3 interaction is probably more apparent than real. The CD2 molecule is proving to be rather complex, with multiple antibody-defined epitopes, an important conformational determinant, and roles in both adhesion and activation (see below). LFA-3 undergoes intriguing regulation of structure by virtue of alternative splicing which creates two different forms of anchorage into the membrane: (1) a conventional transmembrane stretch of amino acids and (2) a phosphatidyl-inositol-linked form[40]. In addition, studies, particularly by Bernard and co-workers, indicate that three other molecules are potentially involved in the CD2–LFA-3 mediated phenomenon of E-rosetting[41]. Perhaps there are additional ligands for CD2 – indeed it has been postulated that a sulfated carbohydrate may be a ligand[42].

## Multiple roles of adhesion molecules in T-cell recognition

How do these molecules participate in T-cell recognition? Recognition involves a complicated cascade of co-ordinated events (Fig. 2) in which adhesion molecules play complex roles: (1) adhesion *per se* is an elaborate multistep regulated process; (2) 'adhesion molecules' can also contribute to signal transduction; and (3) signal transduction via 'adhesion' molecules apparently can be bi-directional between the T cell and the apposing cell.

In our working model, antigen-independent adhesion is the initiating event in T-cell recognition[43,44]. The LFA-1–ICAM-1 and CD2–LFA-3 molecules play a critical role in establishing antigen-independent contact between T cells and potential stimulator/target cells[18,43,44]. We understand this antigen-independent adhesion to be essential: (1) to overcome the mutual repulsion between cells; (2) to intimately appose the plasma membranes of the two interacting cells, and (3) to allow a dwell time during which membrane diffusion will bring the TCR into contact with antigen–MHC which may be present at low concentration on the apposing cell[18]. The strength and character of this initial adhesion depends on many

**Table 1.** Characteristics of adhesion pathways CD2–LFA-3, LFA-1–ICAMs and of the molecules involved

| | CD2–CD58 (LFA-3) | | LFA-1–ICAMs | | | |
|---|---|---|---|---|---|---|
| | Receptor | Ligand | Receptor | | Ligand | Ligand |
| Molecule | CD2 | CD58 | CD11a | CD18 | CD54 | ICAM-2 |
| Alternative name | T11<br>Sheep erythrocyte receptor<br>LFA-2 | LFA-3 | LFA-1 α chain | LFA-1 β chain | ICAM-1 | |
| Representative mAb | 9–6, $T11_1$, OKT11, Leu-5 | TS2/9, G26, BRIC 5 | MHM24, TS1/22 | MHM23, 60.3, TS1/18 | RR1/1, 84H10, WCAM-1, LB2 | None |
| On human chromosome | 1 | 1 | 16 | 21 | 19 | Not known |
| Typical MW | 55 kDa | 70 kDa | 180 kDa | 95 kDa | 80–100 kDa | (28 kDa of protein) |
| Structural homology | To Ig | To Ig | To integrin α | To integrin β | To Ig | To Ig |
| Unique structural features | Intracytoplasmic region is large, highly conserved between species, proline rich | Heavily glycosylated<br>Can be anchored via transmembrane or PI-linked tail | 200 AA 'interactive' domain not shared with integrins<br>Putative cation-binding sites | Cysteine-rich extracellular domain | Heavily glycosylated in a cell-dependent fashion | Homology to distal two domains of ICAM-1 |
| Expression | Primarily T cells | Almost ubiquitous and not generally increased with activation | Widely expressed on cells of hematopoietic lineage | | Restricted but highly inducible by activation, transformation or inflammatory lymphokines | Expression on certain cells such as endothelium<br>Apparently non-inducible |
| Functions | Adhesion<br>Signalling | Adhesion<br>Signalling | Adhesion<br>Signalling | | Adhesion<br>Rhinovirus receptor | Adhesion |
| Divalent cation dependence | None | | Absolute divalent cation requirement. Apparently requirement for $Mg^{2+}$ and additional requirement fulfilled by either $Mg^{2+}$ or $Ca^{2+}$ | | | |
| Temperature effects | Pathway functions at 4°C and 37°C | | Pathway functions at 37°C but not at 4°C with intact cells | | | |
| Situations where one pathway predominates | E-rosetting<br>T-cell binding to cells such as U266 and L428 | | T-cell interaction with endothelium<br>T-cell interaction with monocytes | | | |

parameters including the surface molecules expressed by the apposing cell (see below) and the state of activation of the T cell[18,45].

Triggering can occur only if a sufficient number of T-cell receptors (TCRs) become occupied with specific antigen. However, TCR occupancy resulting in TCR aggregation is a necessary but not sufficient condition for activation[46]. Particularly when the antigen concentration is limiting, co-stimuli from other molecular interactions are required for induction of proliferation or of effector functions such as secretion of lymphokines or release of granules. Facilitating co-signals can be provided by the same molecular pathways that are critical to adhesion. This is certainly true of the CD2–LFA-3 pathway and may well apply to the LFA-1–ICAM-1 pathway. The CD2 molecule is referred to as an alternative pathway of T-cell activation since particular pairs of CD2 mAbs stimulate a variety of T-cell functions[5,47]. It is unclear what the physiological significance of T-cell activation by CD2 *per se* is; however, it is clear that LFA-3 binding to CD2 provides a partial activation signal[48,49] which is dependent on the T-cell antigen–receptor complex[50]. It is also clear that binding of the LFA-1 molecule to its ligand ICAM-1 (or to LFA-1 mAb) provides a potent co-stimulatory signal which synergizes with that provided by CD3 (Ref. 51; van Seventer *et al.*, submitted). Thus, both of these 'adhesion' receptors are also 'signalling' molecules. Such dual function of molecules in adhesion and signal transduction makes sense teliologically, and is proposed for several of the other molecules shown in Fig. 1. Dual function makes sense because the adhesion molecules that are at the cell surface and interacting with other cells are ideally situated to provide regulatory information to the cell. Other examples of adhesion molecules involved in information transduction include: (1) VLA-4 which is part of the integrin family of adhesion molecules, but is proposed to mediate transduction of suppressive signals to the T cell (Ref. 52); (2) CD44 which is involved in T-cell adhesion and homing but also regulates T-cell activation[11].

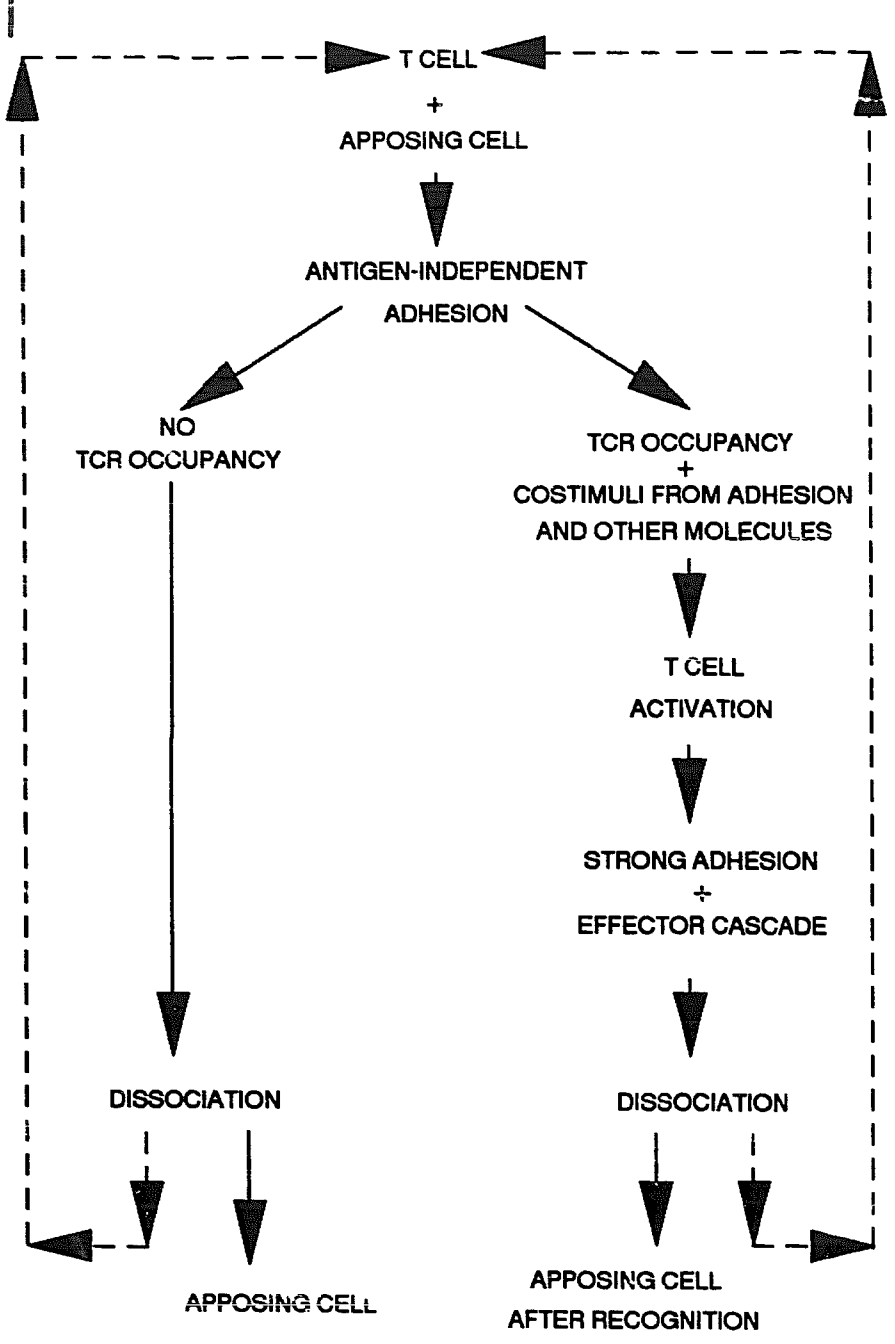


**Fig. 2.** *Model of adhesion-related events in T-cell recognition.*

Another feature of the signal transduction by adhesion molecules is the suggestion that it may involve bi-directional exchange of information. Perturbation of the LFA-3 molecule by LFA-3 mAb can induce augmented secretion of IL-1 from accessory cells[53]. Not only does LFA-3 binding to CD2 convey information to the T cell, that same interaction might convey information to the accessory cell which makes it more efficient in facilitating T-cell activation.

Following T-cell activation, there is a complex cascade of events in the T cell which, for a cytotoxic cell, may culminate in release of cytolytic granules and, for a helper T cell, in the release of helper factors. In both cases there is a period during which there is strong adhesion between the T cell and the apposing cell, in some cases involving formation of an enclosed space between the cells, which may facilitate localized delivery of soluble factors. Although the character of this strong adhesion must differ from the transient adhesion that facilitates initial surveillance, both may depend primarily on the CD2 and LFA-1 pathways. This difference in character appears to be achieved by active regulation of adhesion via these molecules. For example, LFA-1-dependent adhesion can be markedly augmented by treating cells with the phorbol ester PMA, without changing their surface expression of LFA-1 (Ref. 45). Of particular relevance is the recent observation that T-cell receptor cross-linking dramatically but transiently increases LFA-1-dependent T-cell adhesion[17]. Thus, T-cell triggering can result in strengthening and stabilization of LFA-1-dependent adhesion.

The final step in T-cell recognition must be dissociation, in order to allow the T cell to continue to interact with other cells. Much remains to be learned about this process. The termination of strong antigen-specific adhesion may relate in part to the transience of the TCR-mediated augmentation of adhesion mentioned above. Nevertheless, there must be other mechanisms that remain to be elucidated for release of the antigen-nonspecific phase of adhesion.

## Regulation of adhesion

In addition to the rapid regulation of adhesion that may occur during T-cell recognition, adhesion can be profoundly regulated by alterations in level of expression of the receptors on the T cell and their ligands on the apposing cells. On T cells, the level of expression of CD2, LFA-3, LFA-1 and ICAM-1 are all increased following activation; such augmentation presumably contributes to the high frequency of aggregates observed in cultures of stimulated T cells and increases the capacity of activated T cells to interact with other cells *in vivo*. Although some of the augmentation is transient (including part of the increase in LFA-1, CD2 and ICAM-1), some appears to be permanent. Our understanding is that T cells exported from the thymus ('naive cells') express negligible LFA-3 and moderate levels of both CD2 and LFA-1. After stimulation by antigen and subsequent reversion to resting 'memory cells', they have undergone differentiation marked by permanent up-regulation of LFA-3, and modestly (1.5–3-fold) increased levels of LFA-1 and CD2 (Ref. 54). In addition, memory cells generally have increased expression of other adhesion molecules including VLA-4 (CD29, 4B4). Such increased expression of adhesion molecules may explain the augmented adhesion potential of memory T cells. Memory T cells adhere 2–3-fold more than naive T cells to either unstimulated umbilical vein endothelial cells (HUVE) or IL-1-stimulated HUVE[55]. This enhanced adhesion of memory phenotype T cells has been proposed as part of the basis of enrichment of this phenotype at sites of inflammation in autoimmune disease[55–57].

Among the molecules being discussed, ICAM-1 is the most dramatic in its regulation. ICAM-1 expression is induced on many cell types in response to activation, differentiation, inflammatory lymphokines or transformation (Refs 10, 26, 58, 59; Chin *et al.*, unpublished). ICAM-1 is upregulated by IL-1, tumor necrosis factor (TNF), and gamma-interferon (IFN-γ) on dermal fibroblasts[26], synovial fibroblasts (Chin *et al.*, unpublished), and endothelial cells[58]. In contrast, ICAM-1 expression on epidermal keratinocytes is upregulated by IFN-γ and TNF, but not IL-1 (Ref. 59). Cytokine-mediated upregulation of ICAM-1 enhances LFA-1-dependent adhesion of T cells to both endothelial cells and epidermal keratinocytes[59,60].

ICAM-1 expression on monocytes is augmented by

activation and by adherence to fibronectin[61]. Such induction of ICAM-1 on monocytes may play a critical role in antigen presentation by these and other cell types since multiple lines of evidence demonstrate the importance of ICAM-1 in T-cell recognition. For example, antibody to ICAM-1 inhibits antigen-specific T-cell proliferation[61]; furthermore, in a model system in which human allospecific T cells are being stimulated by HLA-DR-transfected murine L cells, transfection of ICAM-1 into the stimulating L cell greatly augments its capacity to induce antigen-specific responses[62].

Of particular interest are *in-vivo* immunohistochemical studies demonstrating that ICAM-1 expression is induced and/or augmented on a variety of cell types at the site of inflammatory responses[63,64]. Such findings are consistent with the presence of inflammatory lymphokines at such sites and with induction of ICAM-1 by such mediators. Furthermore, correlation of T-cell infiltrates with ICAM-1 expression was seen in biopsies from patients with psoriasis, atopic dermatitis, graft-versus-host disease, cutaneous T-cell lymphoma, carcinoma, and autoimmune thyroiditis[34,65]. ICAM-1 expression has also been demonstrated in biopsies of rheumatoid and inflammatory osteoarthritis synovial tissue suggesting that ICAM-1 is involved in T-cell infiltration into inflamed joints[66]. Unlike ICAM-1, ICAM-2 mRNA expression on endothelial cells is constitutively high and non-inducible[36]. Clearly, therefore, the roles of ICAM-1 and ICAM-2 as ligands for LFA-1-dependent T-cell interactions must be quite different with respect to their sites of action and modes of regulation.

## Immune surveillance

As discussed above, antigen-independent adhesion appears to be an early step in engagement between T cells and other cells and thus should be critical in immune surveillance against tumors or virus-infected cells. Such antigen-independent engagement between T cells and tumor cells has been documented in the characteristic rosetting of T cells around Reed–Sternberg cells from Hodgkin's lymphoma, which is mediated largely by CD2–LFA-3 and LFA-1–ICAM-1 interactions[67]. Conversely, downregulation of expression of adhesion molecules by tumor cells may be involved in escape of those cells from immune surveillance. Burkitt's lymphoma cells often express very low levels of LFA-1, LFA-3 and ICAM-1 but acquire high levels of those molecules with multiple passages in tissue culture[68]. Early passage cells are often resistant to lysis by Epstein–Barr virus-specific cytotoxic T lymphocytes but become more susceptible as their expression of (particularly LFA-3) adhesion molecules increases.

Two recent reports raise the possibility of important roles for these adhesion pathways in the dissemination of human immunodeficiency virus (HIV). Infection of T-cell lines or monocytoid cell lines with HIV-1 leads to upregulation of ICAM-1 and LFA-1 (Ref. 69). Furthermore, syncytium formation of HIV-infected cells is blocked by LFA-1 mAb as well as CD4 mAb (Ref. 70).

## Virtues of two adhesion pathways

The CD2–LFA-3 and LFA-1–ICAM pathways of adhesion are both used by T cells in their interactions with a variety of different cell types. However, the target cell plays an important role in determining the contribution of each pathway[18]. In addition to the regulation of ICAM-1 discussed above, there are moderate differences between targets in their expression of LFA-3, which account for some of the differences in utilization of the CD2–LFA-3 pathway[18]. There is also potential for substantial variation between targets in the structure of these (and other) adhesion ligands (for example in their carbohydrate and transmembrane portions), and in the molecules that may interact with them and regulate their adhesion capacity.

The data suggest that both pathways are utilized by the same T cells (rather than some T cells utilizing one pathway and some utilizing another)[18]. Why has evolution provided at least two pathways when one might have sufficed? First, in general, redundancy is often provided in critically important biological systems, so that at least one mechanism will continue to function when unusual circumstances cause the other to fail. Such redundancy in adhesion is consistent with the view that antigen-independent adhesion is critically important to recognition. Second, redundancy allows flexibility in regulation. As illustrated above, ICAM-1 regulation has evolved in such a way that the LFA-1–ICAM-1 pathway may be particularly effective in mediating T-cell surveillance of cells undergoing activation or neoplastic transformation. As the regulation of ICAM-2 expression is explored, it may prove to function in a distinct and specialized way in facilitating particular kinds of recognition. Third, these pathways have important differences as well as similarities. For example, LFA-1 has evolved as a receptor widely used by leukocytes while CD2 has evolved as a receptor used almost exclusively by T cells. Of particular interest are potential differences in the signal-mediating roles of these molecules. During T-cell recognition we hypothesize that the T cell is using multiple surface molecules (potentially including all those shown in Fig. 1) to integrate a great deal of information regarding the apposing cell and to embark on a differentiation pathway tailored to that set of stimuli. The information provided from these two and other 'adhesion' pathways will therefore help determine details of subsequent differentiation including what lymphokines to secrete, what new surface molecules to induce, and where to home to subsequently.

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