REVIEW

The role of ICAM-1 on T-cells in the pathogenesis of asthma

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The role of ICAM-1 on T-cells in the pathogenesis of asthma. L.A. Stanciu, R. Djukanovic. ©ERS Journals Ltd 1998.

ABSTRACT: The capacity of inflammatory cells to adhere is critical to inflammatory responses and involves an array of adhesion molecules grouped into distinct families. Intercellular adhesion molecule (ICAM)-1 has recently attracted much interest in view of increasing evidence that it plays a prominent role in allergic diseases such as asthma and rhinitis. Apart from its role in adhesion of inflammatory cells to vascular endothelium, the extracellular matrix and epithelium, ICAM-1 mediates T-cell/T-cell, T-cell/target cell and T-cell/B-cell interactions.

ICAM-1 on the surface of T-cells is thought to participate in signal transduction and may thus modulate several functions including activation, proliferation, cytotoxicity and cytokine production. Because ICAM-1 is the receptor for the major group of rhinoviruses, the most important cause of acute asthma attacks, binding of rhinovirus (RV) to ICAM-1 on T-cells may, at least theoretically, modulate their function.

We review here the role of ICAM-1 in asthma and focus more specifically on its expression on T-cells. We present evidence for a general increase in ICAM-1 expression in this disease including recent observations of enhanced expression on the surface of T-cells in the airways lumen.

Whilst the implications of intercellular adhesion molecule-1 upregulation in asthma remain to be fully elucidated, its participation in cell trafficking and activation are being considered as a target for treatment. We present here early attempts to interfere with intercellular adhesion molecule-1 as an adhesion molecule involved in cell influx and studies aimed preventing virus-induced exacerbations of asthma in children based on the knowledge that intercellular adhesion molecule-1 is the receptor for rhinoviruses.

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Intercellular adhesion molecule (ICAM)-1 (CD54) is a member of the immunoglobulin gene superfamily and is expressed on endothelial cells, epithelial cells, and fibroblasts, as well as T-cells, B-cells, dendritic cells, macrophages, and eosinophils. It consists of a 76–114 kDa chain glycoprotein, with a core polypeptide of approximately 55 kDa [1], and is composed of one short cytoplasmic, one transmembranous, and five immunoglobulin (Ig)-like extracellular domains. The ligands for ICAM-1 are the β_2 integrins, leucocyte function associated molecule (LFA)-1 (CD11a/CD18) and macrophage antigen (Mac)-1 (CR3, CD11b/CD18) and the rhinovirus (RV). Binding of ICAM-1 to ligand adhesion molecules has profound effects on cell adhesion and activation.

The aim of this article is to review the currently available knowledge of the role of ICAM-1, with special reference to allergic inflammation. Whilst most studies to date have focused on the relevance of its presence on antigen presenting cells and endothelial cells, evidence is now emerging to support a role for ICAM-1 molecules expressed on T-cells in inflammatory responses.

The role of ICAM-1 in T-cell migration

Lung microvascular endothelial cells are important in the adherence and recruitment of circulating lymphocytes

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at sites of antigenic stimulation. The migration of inflammatory cells towards sites of inflammatory responses is a multistep event, involving primary adhesion and rolling, firm adhesion to vascular endothelium and transendothelial migration, which depends upon interactions between the inflammatory cells and endothelial cells, extracellular matrix proteins and locally produced chemokines and cytokines [2, 3]. At the end of a local immune response, when the cytokine and chemokine levels decrease and T-cells become deactivated, the luminal memory T-cells modulate the expression of their adhesion molecules and migrate into the epithelium and back into the circulation via the extracellular matrix. The attachment/capture of flowing cells to the endothelium is the first step in endothelial transmigration, which utilizes ICAM-1, vascular cell adhesion molecule (VCAM)-1 and endothelial (E)-selectin adhesion molecules. The subsequent event of firm adhesion, critical for migration of cells through junctions in the endothelium and to the abluminal surface of blood vessels, is mediated largely by LFA-1/ICAM-1 and very late activation antigen (VLA)-4/VCAM-1 interactions [4]. ICAM-1 can be found present throughout the intercellular junctions of resting endothelial cells that are in contact with migrating T-cells as well on basal surfaces [4]. Most of the ICAM-1 at the endothelial cell surface appears as a homodimer but may also form heterodimers with other

molecules [5]. Endothelial ICAM-1 is up-regulated at the site of inflammation by a host of cytokines. Examples include interleukin (IL)-1, IL-4, tumour necrosis factor (TNF)- α , and interferon (IFN)- γ , which increase *in vitro* ICAM-1 and VCAM-1 expression on vascular endothelial cells [6–8].

Expression of ICAM-1 on T-cells during activation and homing

The migration of T-cells from blood into the lungs constitutes an important component of the inflammatory response in the airways. During this process a series of different surface adhesion molecules are up-regulated and down-regulated, dictating their ability to migrate into lymph nodes and subsequently into inflamed tissue sites. The sequence of up- and down-modulation of adhesion molecules also characterizes their differentiation from naive to effector cells and from naive or effector to memory cells, a process that will dictate the mode of circulation (*via* blood or afferent lymphatics) and tissue localization [9]. L-selectin (leucocyte adhesion molecule-1, LECAM-1, CD-62L) is constitutively expressed on virtually all "naive" 45RA+ T-cells and on a proportion of "memory" 45RO+ T-cells [9, 10].

Naive T-cells migrate from blood into the tissue-associated lymph nodes through postcapillary high endothelial venules to be "instructed" by antigen presenting cells (APCs). Upon antigenic stimulation T-cells shed L-selectin and acquire other adhesion molecules such that, *e.g.*, activated cytotoxic T-cells express high levels of ICAM-1 as well as LFA-1 (CD11a/CD18), and VLA-4 (CD49d/CD29) [11, 12].

Under the influence of cytokines and chemokines produced in inflamed tissue, the "memory" T-cells adhere and migrate through the endothelium which expresses increased amounts of ICAM-1 and VCAM-1 [2, 7]. ICAM-1 is expressed on a minority of blood T-cells, but is upregulated several-fold on T-cells in the airways lumen with further upregulation being seen in inflammatory conditions such as asthma [13].

After cessation of the antigenic stimulus, resting, long-lived memory T-cells leave the tissue by the afferent lymphatics into the tissue draining local lymph nodes [9] and recirculate. It is thought that memory/effector T-cells preferentially express homing receptors that return them to the same tissue where they were first activated and where there are complementary ligands, "addressins", on the capillary endothelium [2]. Selective lymphocyte homing receptors, such as the cutaneous lymphocyte antigen (CLA) on T-cells binding to E-selectin [14], have been found. It is unclear which homing adhesion molecules are involved in migration of T-cells into the lung mucosa. Similarly, the fate of ICAM-1 on recirculating T-cells is unknown.

In addition to utilizing the adhesion molecules on endothelial cells as an anchor, T-cells may bind to the immobilized chemokines on the cell surface of endothelial cells or to the extracellular matrix [15, 16] and respond chemotactically to a variety of chemokines including IL-8, regulated on activation, normal T-cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1 α and β , monocyte chemotactic peptide (MCP)-1, -2 and -3, lymphotactin, eotaxin or the cytokines IL-2 and IL-15

[17–24] (fig. 1). Chemokines may direct T-cell migration by activating the surface integrins and by inducing transendothelial migration and further chemotaxis through tissues [3, 25–29]. A number of chemokines induce the formation of cytoplasmic uropods and redistribution of several adhesion molecules including ICAM-1, -2, -3, and CD44 to this structure. This promotes cell-cell contact, and increased T-cell migration into tissues [3, 22, 30, 31]. Most of the chemokine receptors are up-regulated on the CD45RO+ memory/activated T-cells and there is a selective attraction of T-cells of memory/activated phenotype by chemokines [23, 32–34]. Chemokines MIP-1 α , MIP-1 β , RANTES, and interferon-inducible protein (IP)-10 cause increased *in vitro* adhesion of both resting and anti-CD3-activated T-cells to recombinant human (rh) ICAM-1 and rhVCAM-1 and to extracellular matrix proteins, and this is accompanied by increased affinity of the integrin molecules [3]. In experimental conditions there is a proteolytic cleavage and shedding of the adhesion molecules redistributed at the level of the cellular uropod [35, 36].

The role of ICAM in T-cell function: antigen-presentation, activation, proliferation, cytotoxicity, and cytokine production

ICAM-1 on APCs

T-cell activation requires T-cell receptor (TCR) engagement by antigen and interaction between costimulatory molecules on T-cells and their ligands on APCs [2]. Interaction between ICAM-1 and its ligand LFA-1 may be bidirectional in that both can be expressed by T-cells as well as some APCs. However, the role of ICAMs in T-cell activation, proliferation and cytokine production has been studied mainly in the context of its expression on the surface of APCs. In this context it can act as the sole accessory molecule participating in antigen-specific T-cell activation [37], although additional interaction between other accessory molecules, CD28 or cytotoxic T-lymphocyte-associated antigen (CTLA)-4 and CD80 antigen on B-cells (B7-1), is required for an optimum response [37]. Plate-bound ICAM-1 and ICAM-3, together with anti-CD3 or anti-TCR $\alpha\beta$ monoclonal antibodies (mAb) induce expression of the IL-2 receptor (IL2R α , CD25) and cell proliferation [38–40].

The relevance of ICAM-1 expressed on APCs in determining the cytokine profile in disease is unknown. *In vitro* costimulation of resting human CD4+ T-cells by immobilized anti-CD3 and ICAM-1 increases the release of IL-4, IL-2 and granulocyte/macrophage colony-stimulating factor (GM-CSF) [41]. However, in healthy subjects "naive" and "memory" human CD4+ T-cells costimulated with anti-CD3 and purified ICAM-1 produce different cytokines: CD45RA+ cells produce only IL-2 whilst CD45RO+ produce IL-2, IFN- γ , GM-CSF and low levels of IL-4 [42]. In contrast, repeated costimulation with ICAM-1 of CD4+ CD45RO+ T-cells, but not CD4+CD45RA+, induces significant levels of GM-CSF and IFN- γ , which resembles a Th1-like cytokine pattern. This is associated with a pronounced reduction in expression of CD60, a marker for Th2-type cells.

Fig. 1. – Intercellular adhesion molecule-1 (ICAM-1) expression in the bronchial mucosa during activation of circulating T-cells and their migration into the site of allergen exposure. Increased production of cytokines and chemokines leads to: 1) increased ICAM-1 expression on endothelial cells and T-cells in the mucosa and bronchial lumen; 2) induction of high affinity leukocyte function associated molecule (LFA)-1 on T-cells with firm adhesion to the endothelium; 3) development of a cytoplasmic uropod on T-cells adhering to the endothelium which extends towards the vascular lumen and contains regrouped adhesion molecules to enhance the capture and transmigration of other circulating T-cells by ICAM-1/LFA-1 interactions; 4) increase in soluble ICAM-1 (sICAM-1) levels that may cause de-adhesion and migration of T-cells. The T-cells transmigrate towards the extracellular matrix and into the airway where increased levels of sICAM-1 can be detected due to shedding from T-cells and other cells. $\triangle$: ICAM-1; $\square$: LFA-1; T: T-cell; E: eosinophil.

T-cell activation

The presence of ICAM-1 on T-cells may play an important role when the expression of other costimulatory molecules on T-cell is suboptimal. Recent evidence, such as the finding of tyrosine phosphorylation induced by cross-linking of ICAM-1 or ICAM-3 on T-cells, supports a role for surface ICAMs in T-cell activation [43]. ICAM-1 is weakly expressed on resting T-cells, in contrast to ICAM-3 which is expressed at higher levels [44]. Adhesion of resting T-cells to LFA-1 occurs primarily *via* ICAM-3 followed by ICAM-1, which establishes more stable cell-cell interactions [44, 45]. ICAM-1 is the major ligand for LFA-1 on activated T-lymphocytes [46]. Anti-ICAM-3 and anti-CD3 mAbs induce the strong expression of the activation marker CD25 on both resting and activated T-cells. In contrast, anti-ICAM-1 antibodies are costimulatory with anti-CD3 antibodies for CD25 expression only on activated T-cells [45].

Cytotoxicity

Studies using blocking by antibodies suggest that two sets of adhesion molecules are important for cytotoxic T-cell/target cell interaction: LFA-1/ICAM-1 and CD2/LFA-3. Homotypic (T-cell-T-cell) adhesion of lymphocytes,

which is dependent on LFA-1 and ICAM-1, is important for cytotoxic T-cells. Contact of TCR on T-cells with cells bearing antigen generates intracellular signals that lead to the conversion of LFA-1 to a high-affinity state and regulates LFA-1/ICAM-1-dependent adhesion [2]. Whereas past emphasis was placed on ICAM-1 on target cells, evidence now points to a potential role in cytotoxicity for ICAM-1 expressed on T-cells. The presence of ICAM-1 on CD8⁺ T-cells correlates with cytotoxic activity and production of IFN- γ [12]. A proportion of ICAM-1⁺ cells belong to CD3⁺/CD8⁺/CD28⁻ T-cells which do not express antigens associated with acute cell activation (IL2R, human leucocyte antigen (HLA)-DR) [47]. These cells have recently been shown to possess a functional CD3/TCR complex and are capable of *in vitro* anti-CD3-induced redirected cytotoxicity [47]. Importantly, they are anergic to anti-CD3-induced proliferation, which is in keeping with reduced proliferative responses of bronchoalveolar lavage (BAL) T-cells. Furthermore, these cells may be important in responses to recall viral antigen.

Cytokine production

Emerging evidence suggests that ligation of ICAM-1 on T-cells can have an important effect on cytokine production.

Co-engagement of CD3 with ICAM-1 enhances the activation of murine CD4+ and CD8+ T-cells in an accessory cell-free culture system and induces production of IL-3 and IFN- γ , which is four times greater in CD8+ T-cells compared to CD4+ T-cells [48]. Anti-ICAM-1 mAb inhibits *in vitro* production of TNF- α , IFN- γ and IL-1 by phytohaemagglutinin (PHA)-activated human T-cells [49]. Furthermore, there is evidence that costimulation of T-cell clones producing either Th0 or Th2 type cytokines with anti-CD3 and anti-ICAM-1 mAb enhances the production of IL-4 [50]. Interestingly, costimulation with anti-ICAM-1 and anti-CD3 protects T-cell allergen-specific clones from apoptosis induced by anti-CD3 [50].

Helper activity for B-cells

Interaction between LFA-1 expressed on B-cells and ICAM-1 on activated T-cells is important in early events of T-cell-dependent B-cell activation, proliferation and differentiation [51]. In mice, an antibody against the α -chain of LFA-1 mimics the IL-4 growth factor effect on B-cells inducing increased levels of major histocompatibility complex class II molecule (Ia) expression, costimulating proliferation with anti-immunoglobulin (Ig) D heavy-chain molecules on B-cells (anti- δ), and inducing lipopolysaccharide-activated B-cells to secrete IgG1 [52].

Modulation of ICAM-1 on T-cells

ICAM-1 is expressed at a low level on a proportion of resting T-cells and appears constitutively avid for LFA-1 [11, 53, 54]. A low percentage of circulating blood T-cells expresses ICAM-1 in contrast to the high levels of LFA-1 expression [13]. Mitogen and antigen-specific stimulation [55], cytokines (IFN- γ , IL-1 β , IL-2 and TNF- α) [11] and viruses [56, 57] may all cause up-regulation of ICAM-1 on the T-cell surface. *In vitro*, T-cell activation by mitogen gradually increases ICAM-1 expression from 15 to 80% of T-lymphocytes over the course of 2–3 days of culture [58]. The kinetics of up-regulation and maintenance of expression of ICAM-1 on both CD45RA+ and CD45RO+ subsets in PHA-stimulated purified T-cells is very similar: maximum expression of both ICAM-1 and IL-2R α correlates with the time of peak proliferation (day 3–4) [54]. However, whilst levels of CD25 on CD45RO+ T-cells begin to decrease after 3 days those of ICAM-1 are high even after 11 days [54], suggesting that ICAM-1 may play a role in the effector and regulatory functions of T-cells. Similarly, the *in vitro* kinetics of ICAM-1 expression on T-cells following antigenic stimulation are similar to those observed for IL-2R α , being maximum between 7 and 10 days and correlating with the magnitude of the proliferative response [55].

Upregulation of ICAM-1 on T-cells can also be observed following exposure to both live and inactivated viruses. Thus, by stimulating T-cells from seropositive patients with inactivated cytomegalovirus (CMV), the expression of ICAM-1 is increased on both CD4+CD45RO+ and CD8+CD45RO+ after 6 days of culture, mimicking kinetics similar to those of soluble antigens [57]. In mice systemically infected with lymphocytic choriomeningitis

virus ICAM-1, VLA-4, and LFA-1 are up-regulated on splenic CD8+ T-cells, and this has been shown to correlate with T-cell mediated meningeal inflammation, suggesting a role for these adhesion molecules in extravasation of activated T-cells to inflammatory foci [56].

Soluble ICAM-1

A circulating, soluble form of ICAM-1 (sICAM-1) has been detected in culture supernatants and human body fluids and is thought to be derived through shedding of surface ICAM-1 [59]. The molecular mass range of sICAM-1 is in the expected range for monomeric ICAM-1 [59]. The mechanism of ICAM-1 shedding from the cellular membrane is poorly understood. It is possible that activation of the cells induces the expression or activity of a cell membrane protease which is able to cleave membrane-bound ICAM-1. The physiological range for circulating sICAM-1 is between 102 and 450 ng·mL⁻¹ [36]. GANPUL *et al.* [60] have recently demonstrated that cell surface LFA-1 cannot bind sICAM-1 at physiological concentrations or particles bearing physiologic densities of ICAM-1 <1 μ m in diameter. Thus T-cell adhesion is not inhibited by physiological levels of sICAM-1.

In culture the levels of sICAM-1 correlate with the degree of immune cell activation and seem to be an early and sensitive marker for activation of both T-cells and B-cells. Levels of sICAM-1 correlate with the amounts of soluble IL-2R, soluble CD23 shed by B-cells and IL-4 produced by normal peripheral blood mononuclear cells cultured in the presence of PHA [61]. In a murine model of lymphocytic choriomeningitis virus infection, a marked virus-induced elevation in circulating sICAM-1 has been observed, the presence of which coincides with the phase of virus-induced T-cell activation, but well before maximum cell activation can be demonstrated [62].

The role of sICAM-1 remains to be fully elucidated. Several studies suggest that sICAM-1 may participate in a feedback down-regulatory mechanism. *In vitro*, recombinant sICAM-1 are able to inhibit homotypic T-cell aggregation, cytolytic interaction between cytotoxic cells and target cells, major histocompatibility complex (MHC)-restricted cytotoxicity, antigen-induced proliferation and antigen-triggered induction of cytokines in T-cells [36, 63–66].

The monomeric forms of sICAM-1 bind to the receptor LFA-1 with extremely low affinity [5]. It has been found that the levels of dimerization of ICAM-1 shed *in vitro* directly correlate with enhanced binding to LFA-1 [5, 67]. Multimeric forms of ICAM-1, shed from the cell surface and concentrated at sites of inflammation, may bind to LFA-1 with sufficient affinity to interfere with the local immune response [66]. The shedding of functional sICAM-1 after T-cell activation may thus help end the local immune response by blocking cell-cell interactions.

In addition, sICAM-1 may have a protective effect by interfering with the binding of RVs to cell surface ICAM-1 as these use ICAM-1 as their anchor during binding to cells. It has been found that recombinant soluble dimeric forms of sICAM-1 have a higher anti-rhinoviral activity *in vitro* than monomeric sICAM-1 [68, 69].

ICAM-1 in allergic inflammation and asthma

Evidence accumulated to date has shown a prominent role for ICAM-1 in allergic inflammation. Asthma is a chronic inflammatory disease characterized by accumulation of activated eosinophils and T-lymphocytes in the bronchial mucosa. Lung cell infiltration in asthma is regulated by several pathophysiological mechanisms, including increased expression of cell adhesion molecules and levels of chemoattractants. Several studies have shown prominent upregulation of ICAM-1 in asthmatic airways. Increased ICAM-1 expression in asthma has been reported on eosinophils [70], T-cells [71], and bronchial endothelial [72] and epithelial cells [73].

Lung microvascular endothelial cells are important in the adherence and recruitment of circulating lymphocytes to sites of allergen exposure. Immunoelectron microscopy for ICAM-1, VCAM-1 and E-selectin has demonstrated *de novo* synthesis of these molecules and their expression along the luminal cell membrane of endothelial cells, suggesting that ICAM-1, VCAM-1 and E-selectin are continuously synthesized as part of the inflammatory response in asthma [74]. The effect of allergenic stimulation on ICAM-1 expression has been studied. Six hours following allergen challenge of asthmatic airways *via* the fibre-optic bronchoscope there is a striking increase in ICAM-1 and E-selectin expression on the endothelium which is associated with an influx of neutrophils, mast cells, eosinophils, and T-cells [75]. Whilst in mild asthma the baseline expression of endothelial ICAM-1 may [76] or may not be increased [77], our studies of severe asthma demonstrate a consistent increase in the number of postcapillary venules staining positively for ICAM-1 despite the use of high doses of inhaled and oral corticosteroids. Together with the finding of enhanced ICAM-1 immunostaining in perennial allergic rhinitis [78], a more severe form of allergic rhinitis, this would suggest that severe mucosal inflammation is associated with a clear upregulation of this adhesion molecule which may, at least in part, explain the persistence of cellular recruitment, inflammation and the extent of disease severity.

ICAM-1, VCAM-1 and E-selectin are constitutively expressed on the epithelium of the bronchial mucosa both in normal subjects and patients with either atopic or non-atopic asthma [72], but their expression is more pronounced in asthmatics than control subjects [73, 76, 79, 80]. In patients with allergic asthma, a further significant increase in ICAM-1 expression occurs after allergen challenge [81].

The factors determining expression of ICAM-1 on peripheral blood T-cells have been investigated in a number of studies but remain poorly understood. In one study the expression in mild atopic asthmatics was increased as compared with healthy subjects and severe asthmatics. This would suggest that ICAM-1 upregulation on blood T-cells is a feature of atopic asthma. In severe asthma these cells migrate selectively from the circulation into the tissues where they form an integral part of the inflammatory response [82]. In another study, asthmatics who were found to develop dual responses following allergen inhalation had a significantly higher expression of ICAM-1 on both CD4+ and CD8+ T-cells as compared with both single (early phase only) responders and control subjects [71]. In these subjects allergen challenge caused

a decrease in CD8+ICAM-1+ T-cells at the time of the late response as a consequence of either a selective migration of these cells into the airways or shedding of ICAM-1 from the cell surface as suggested by the significant rise in serum levels of sICAM-1 [71].

The expression of ICAM-1 on airways T-cells has also been studied. In ovalbumin-sensitized and challenged mice, 50–90% of lung tissue and BAL T-cells expressed ICAM-1, together with LFA-1 and VLA-4 [83]. Recently, we have found that by comparison with blood in which expression of ICAM-1 is low, a greater proportion of CD3+ T-cells in induced sputum express ICAM-1 in both normals and mild asthmatics [13]. The greater than 10-fold proportion of ICAM-1+ T-cells in the airways of asthmatics as compared with peripheral blood suggests that ICAM-1 on T-cells is either up-regulated during transmigration and activation of T-cells in tissues and/or that ICAM-1+ T-cells are preferentially attracted. Consistent with T-cell activation in asthmatic airways we have found that by comparison with sputum cells from healthy non-atopic individuals, the proportion of ICAM-1+ T-cells in asthmatics is enhanced twofold with a median of 46% of T-cells being positive by flow cytometry [13]. The implications of these observations for mechanisms of asthma and responses to RVs remain to be elucidated. Given that ICAM-1 is a receptor for RVs [84], a major cause of asthma exacerbations both in children and adults [85, 86], its heightened expression in asthma could provide the basis for the increased susceptibility of asthmatics to respiratory infections.

Levels of serum sICAM-1 and soluble E-selectin (sE-selectin) are higher in stable asthmatics as compared with controls, and are further increased in acute asthma [87–89]. A rise in sICAM-1 occurs both in the serum and BAL of atopic asthmatics 18 h after allergen challenge [90]. We have found increased levels of sICAM-1 in sputum in asthmatics, as compared with levels from non-atopic healthy subjects [13]. The origins of sICAM-1 and implications of increased levels in sputum in asthma are unclear. Increased ICAM-1 expression might result from chronic antigen stimulation, stimulation of cells by trypsin [91], and cytokines TNF- α , IL-2 and IFN- γ , or may be due to infection by viruses. Of further relevance to allergic inflammation is the finding that sICAM-1 can activate eosinophils to secrete cationic proteins [92] which are toxic to the bronchial epithelium and are believed to be central in causing epithelial damage that is a characteristic of asthma.

Therapeutic perspectives

In view of the role played by ICAM-1 in T-cell transmigration at sites of allergic exposure, there are potential therapeutic implications of targeting ICAM-1 in an attempt to prevent the recruitment of T-cells and other cells bearing LFA-1 which utilize this adhesion molecule. A number of approaches have been developed [93] to either inhibit the expression of ICAM-1 (using antisense oligonucleotides) or interfere with interaction between ICAM-1 and its ligand. The latter approach has been shown to be effective in animal models of autoimmune diseases. Of relevance to asthma treatment is the finding that administration of anti-ICAM-1 in monkeys sensitized by *Ascaris*

inhibits eosinophilic infiltration of the airways, as assessed by BAL, and the rise in airways responsiveness that results from intratracheal aerosolization [94]. This effect, however, has not been consistently reproduced. In a murine model the inhibition of eosinophil recruitment required the combination of anti-LFA-1 and anti-ICAM-1 mAb [95]. In another study using Norway rats, administration of an anti-ICAM-1 antibody induced a reduction in hyperresponsiveness but not in airway inflammation [96]. Together these studies do not suggest that targeting ICAM-1 is likely to lead to a suitable therapy, at least if this approach is used in isolation.

More optimistic results have been obtained with sICAM-1 as a means of preventing infection with RVs. The truncated soluble form of ICAM-1, tICAM₄₅₃, has been successfully used to inhibit infection with the RV16 serotype in chimpanzees [97], but the implications of this study for prophylaxis of RV infections in humans, the most common cause of asthma exacerbations, remain to be seen. Recent *in vitro* studies have shown that loratidine, a new generation antihistamine, is able to attenuate by as much as 80% the epithelial expression of ICAM-1 induced by RV16 [98]. In addition, this drug inhibits histamine- [99] and IFN- γ -induced ICAM-1 expression on nasal epithelial cells and skin keratinocytes [100], respectively. Together these studies have provided the rationale for a series of studies called "Preventia" which are currently being conducted with the aim of appraising the clinical relevance of these *in vitro* observations, more specifically assessing the capacity of loratidine to prevent virus-induced exacerbations in children and deteriorations caused by air pollution.

Conclusions

Abundant evidence points to an important role for intracellular adhesion molecule-1 in asthma. Its up-regulated expression on a variety of both structural and inflammatory cells in this disease would suggest a common mechanism, probably involving the transcription factor nuclear factor- κ B. In addition to what has been known about its expression on endothelial and epithelial cells, it is now increasingly appreciated that this adhesion molecule may have a prominent role in the activation of T-cells and their functions. The full implications of intercellular adhesion molecule-1 present on T-cells should therefore stimulate further research both in normal and allergic immune responses such as those that characterize atopic asthma.

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