

## Review article

# Adhesion molecules of allergic inflammation: recent insights into their functional roles

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As a rule, inflammation is characterized by the accumulation of leukocytes at the site of injury or infection. Allergic reaction typically induces inflammation, which should be regarded as a hallmark of the allergic disease. The recent huge harvest of information about the molecular processes which govern the emigration of leukocytes from blood vessels and their consequent accumulation at sites of inflammation has completely modified our understanding and will probably lead to new strategies in the treatment of both acute and chronic inflammation (4, 20, 27, 32, 59). At present, therapeutic strategies to cure allergic inflammation should be considered to be the proper approach to the treatment of allergy. In fact, the allergist's task is to prevent the irreversible effects of untreated subacute or chronic inflammation, i.e., the "remodeling" of the histologic structure that leads to permanent anatomic and functional damage (34). The new insights into the precise molecular processes leading to inflammation can aid strategies to prevent the possible damage caused by allergic reaction.

We present here the current understanding of the pathogenesis of allergic inflammation with respect to the function of adhesion molecules (AM) involved in

this process, and of how the drugs now used to treat allergies affect AM.

## General features of AM

Localization and migration of immunocompetent cells into different tissues require, firstly, adhesion to the endothelium and, next, locomotion to the target tissue, each stage of the process depending upon intercellular and cell/matrix adhesion.

The number of known cellular surface molecules involved in adhesion is as large as their structures are diverse. AM are grouped in the following distinct families, depending upon structural analogies (24, 54): 1) the immunoglobulin superfamily (Ig), which is characterized by a variable number of Ig-like domains (among them, ICAMs, VCAM1, N-CAM, LFA3, CD2, and CD28); 2) the integrins, heterodimeric molecules composed of non-covalent-linked  $\alpha$ - and  $\beta$ -chains (to date, seven  $\beta$ - and 10  $\alpha$ -chains have been described); and 3) the selectins (L, E, and P), which are characterized by an *N*-terminal lectin-like domain. However, some other important AM (e.g., CD44) are not classified in these families (4, 24, 54).

It is apparent that the adhesion machinery is complex and highly flexible: for instance, there are frequent interactions and overlapping between different pairs of ligands; e.g., a single molecule may have two or more counterparts (22, 54). Some molecules are constitutively expressed, but their surface density and ligand affinity may be modulated by other molecular interactions (24, 26). In addition, some AM are upregulated by cytokines such as IFN- $\gamma$ , proinflammatory cytokines (25), or even regulatory cytokines such as IL-4 (42, 53, 57). Different adhesion systems are different in their temperature and divalent cation dependency (24).

### General features of AM role in allergic inflammation

Calderon & Lockey (12) recently reviewed the possible role of AM in asthma, as previously studied in allergy by Gundel et al. (32) and Bagnasco et al. (4). On the basis of these reviews, we have also reassessed the model of the various stages of allergic inflammation, as shown in Fig. 1.

Leukocyte extravasation must be regarded as a crucial stage in leukocyte localization in a given tissue: it requires a direct interaction with endothelial cells which is mediated by AM. This cell-to-cell interaction is the first stage, and it is regulated by

selectins. It should also be considered, as far as the allergic reaction is concerned, that the huge release of histamine leads to vasodilation, resulting in a slower blood flow through the vessels. This phenomenon enhances the opportunity of leukocytes to roll along the endothelial wall, constitutively expressing selectins, as previously mentioned.

L-selectin was first shown to permit adhesion of lymphocytes to peripheral lymph nodes (30, 33). More recently, it has been also shown to mediate "rolling" of neutrophils along the walls of the microvasculature, a phenomenon which may be the first step in the accumulation of leukocytes at sites of inflammation (39).

The rolling of leukocytes along the wall of the vessels is necessary for stronger adhesion at sites of inflammation. P-selectin, very rapidly expressed by endothelial cells, mediates "rolling" of leukocytes at inflamed sites and can tether leukocytes to the endothelium. The relatively loose association of leukocytes with the endothelium mediated by P-selectin permits the development of the stronger heterotypic adhesion mediated by the interaction of leukocyte  $\beta_2$ -integrins with ICAM-1 on the endothelium (48).

E-selectin is expressed on the endothelium within 2 h of stimulation, and it adheres to sialylated Lewis X sugars of leukocyte surface glycoproteins (29, 50, 58). Adhesion between ICAM-1 on the endothelium

### Involvement of adhesion machinery in the different stages of allergic inflammation

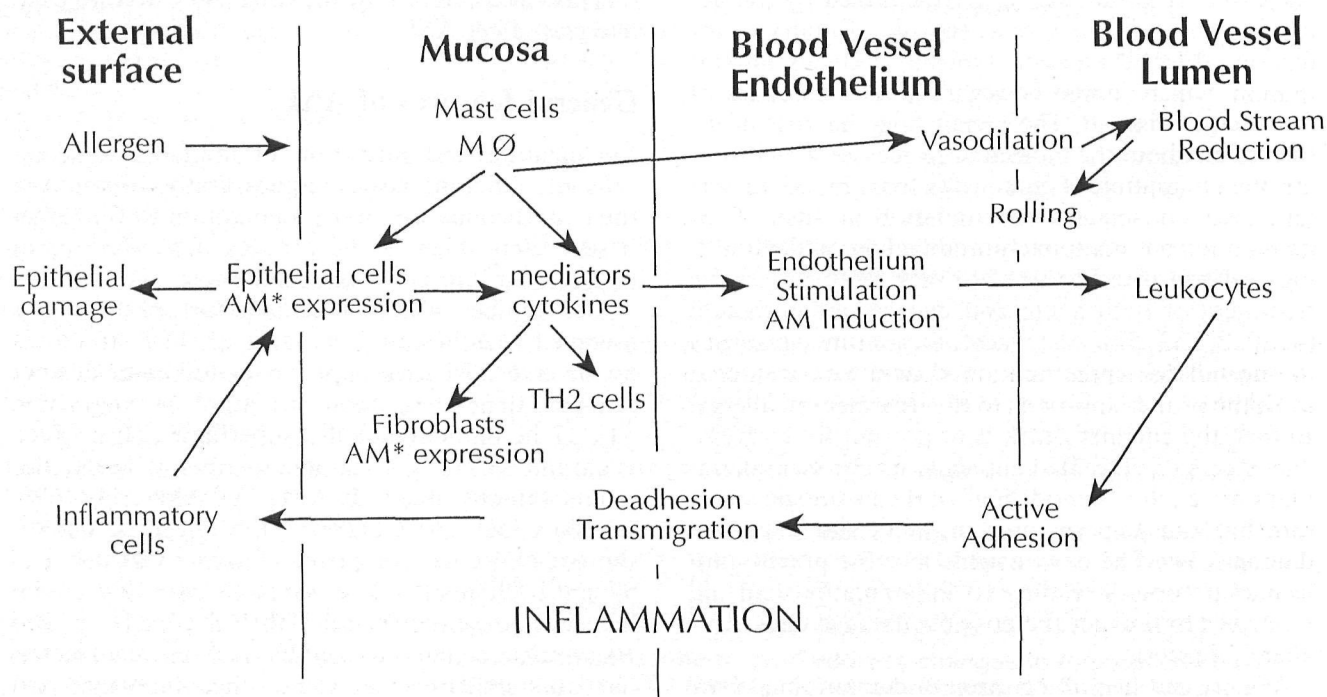


Fig. 1. Revised and integrated version of what Calderon & Lockey (12) recently proposed (explanations in text). AM = adhesion molecule; MØ = monocytes/macrophages.

and  $\beta_2$ -integrins on leukocytes is facilitated after selectin interactions.  $\beta_2$ -integrin-ICAM-1 adhesion appears to be critical for migration of leukocytes into the junctions between the endothelial cells and, ultimately, to the abluminal surface of the blood vessels.

The increased expression of ICAM-1 and VCAM-1, which follows E-selectin expression, attracts mononuclear cells to inflamed sites; this explains why mononuclear cells can reach inflamed sites only after neutrophils (30, 40, 48). The further stages are deadhesion and transmigration through the blood vessel wall to the site of inflammation, and these are regulated by integrins (LFA-1, VLA-4) and their ligands (ICAM-1, VCAM-1).

Fig. 1 summarizes the most important stages of allergic reaction and inflammation, since the allergen interacts (through IgE) with cells releasing mediators and cytokines. These soluble factors act on different targets, including endothelial cells, which thus initiate the inflammatory process. Through all these subsequent stages, inflammatory cells reach the mucosa surfaces, where they can be observed; for instance, in BAL (bronchoalveolar lavage) fluid of asthma (10), nasal lavage fluid in rhinitis (45), and lacrimal fluid in conjunctivitis (9, 52).

Each stage has been investigated in depth, but the processes involving the epithelium, the topic that we consider to be of great basic and clinical relevance, will be developed in a separate part of the present article.

### Epithelial cells, adhesion molecules, and inflammation

The first *in vivo* experimental evidence that epithelial cells can express ICAM-1 upon allergen stimulation was provided by Wegner et al. in 1990 (59) in a primate model of asthma. Despite this promising and exciting demonstration, very few studies have been done on this topic in man. As far as asthma is concerned, Montefort et al. (44) reported the presence of ICAM-1 on epithelial cells of both asthmatic patients and controls, whereas Campbell et al. (13) found ICAM-1 presence on bronchial epithelium of asthmatic subjects in primary culture upon histamine supplementation.

Since epithelial cells should not be considered to be merely passive participants in this complex process, i.e., as "bystander" cells or simply targets for cytokine action, we designed two experimental approaches: one "*in vitro*" and the other "*in vivo*".

Five different epithelial cell lines of different origins (bronchus, intestine, conjunctiva) have been tested in culture; all of them constitutively express ICAM-1, although to variable degrees. The presence of this molecule can be upregulated on the cell mem-

brane by different stimulations such as PMA or different cytokines, e.g., IFN- $\gamma$  (14).

For the *in vivo* studies, a conjunctival allergen-specific challenge has been adopted, since epithelial cells can be easily collected, it is possible to monitor the reaction at different time intervals, and, most important, the contralateral eye may be used as control.

Clear evidence that ICAM-1 can be expressed by conjunctival epithelial cells upon allergen-specific stimulation has been provided by Ciprandi et al. (15). In this study we demonstrated no ICAM-1 expression at base line in normal subjects or in pollen-sensitive subjects (the study has been performed in symptom-less subjects out of pollen season). The latter subjects expressed only high levels of ICAM-1 upon specific allergen challenge: the ICAM-1 presence on conjunctival epithelial cells was obviously related to the clinical variables and the inflammatory cells in the conjunctiva after allergen stimulation. We documented also the kinetics of the appearance of the AM upon allergen stimulation, with the unexpected finding of an early (30-min) appearance of ICAM-1 on epithelial cells. The persistence of the molecule was then monitored for up to 48 h. We have not yet found a satisfactory explanation for such an early expression, although we proposed some explanations (4).

Additional studies have confirmed our ICAM-1 findings also on the nasal epithelium of allergic subjects upon allergen-specific stimulation (Ciprandi et al., submitted). Notably, in another study (17), we demonstrated that histamine, by itself, is not able to induce ICAM-1 on cell membranes. Since we believe that allergen-specific challenge is a very fruitful model, a tool for clinical and research purposes, but still just a model, we designed a study to detect ICAM-1 expression on conjunctival and nose epithelial cells upon natural exposure to allergen. For this purpose, we studied *Parietaria judaica*-sensitive patients out of the pollen season (when symptom-free) and during the pollen season. As expected, ICAM-1 was detectable on epithelial cells during the pollen season only (Ciprandi et al., submitted).

Several questions arise from all these findings: 1) Are the epithelial cells actually able to express ICAM-1, or is the molecule source a process of shedding, by inflammatory cells, for instance, since epithelial cells have been found bearing only ICAM-1 on their surface? 2) What is the function of ICAM-1 on epithelial cells in allergy? 3) Could ICAM-1 on epithelial cells be a useful marker to monitor allergic reaction, or could it have clinical relevance? Three experimental demonstrations allow us to state that epithelial cells themselves express ICAM-1. Firstly, ICAM-1 expression and upregulation *in vitro* on epithelial cell lines has been shown in the absence of

any other possible source of soluble ICAM-1 (14). Secondly, Kvale et al. (37) demonstrated by Northern blot analysis the ICAM-1 mRNA induced by IFN- $\gamma$  in a colonic epithelial cell line. Finally, very recently, in our laboratory, by means of *in situ* hybridization, Pesce & Fiorino demonstrated ICAM-1 mRNA in the human W-K conjunctival cell line. They also obtained preliminary evidence of ICAM-1 mRNA in conjunctival epithelial cells obtained after allergen-specific challenge (paper in preparation).

The presence of ICAM-1 on epithelial cells should be considered from different perspectives. Firstly, the phenomenon may reveal epithelial cell activation, with possible direct involvement in the allergic inflammation. For clarification of this point, the possible relationships between ICAM-1 expression and cytokine release by epithelial cells should be investigated. A second possibility is that the ICAM-1 presence reveals an enhanced susceptibility of epithelial cells to be damaged by the offending cells of allergic inflammation (e.g., eosinophils). This hypothesis might provide an additional pathogenic explanation of the epithelial damage which is one of the hallmarks of the allergic inflammation. The presence of ICAM-1 on epithelial cells may definitely be considered to be a marker of inflammation caused by allergic stimulus.

A further function of ICAM-1 on epithelial cells in the respiratory tract may be as a virus receptor. In fact, the first domain of the ICAM-1 molecule has been shown to be the major human rhinovirus receptor (31, 55). The following considerations prompted us to elucidate this topic further: other AM are known to be receptors for virus proteins, e.g., CD4 as a receptor for HIV gp 120 protein (21, 46); and epithelial cells are known to bear other virus receptors; e.g., CD21 as an Epstein-Barr virus receptor, previously found on B cells, has been described and functionally characterized on epithelial cells (7). A prerequisite for a clinical relevance of ICAM-1 on epithelial cells as virus receptor is the cellular polarity of its expression. Recently, Albelda (2) demonstrated that this molecule is expressed on the luminal surface on both epithelium and endothelium.

The role of virus infections (11) as precipitants of asthma symptoms, from epidemiology, through clinical and laboratory findings up to molecular biology, has recently been extensively and very cogently reviewed by Bardin et al. (5), Johnston et al. (35), and Pattemore (47). Their papers provide new insights into the relationship between viruses and asthma, as they critically reviewed the methods of virus detection and identification in the various studies, concluding that most of them drew conclusions on the basis of unreliable or invalid experimental procedures. In fact, we can draw some conclusions from

their studies: the influence of virus infections in asthma attacks reaches to as many as 50% of cases, at least in childhood; on the other hand, asthmatic children more frequently suffer from respiratory viral infections than do controls, and these infections are almost entirely due to rhinovirus (47).

What are the mechanisms of viruses as precipitants of asthma symptoms? Bardin et al. (5) report direct effects on the lower airways or remote mechanisms, both categories including several mechanisms whereby viral infections may lead to exacerbation of asthma: nevertheless, there is no definite proof of these processes.

## The minimal persistent inflammation

A minimal persistent inflammation has been described in asthmatic subjects during clinical latency of the disease (23, 34). We related this concept to an experimental finding that mite-sensitive subjects, although completely symptom-free, at base line showed a mild expression of ICAM-1 on conjunctival epithelial cells.

These observations prompted us to study a group of healthy volunteers, a group of pollen-sensitive subjects (out of pollen season) symptom-free for months, a group of mite-sensitive patients during clinical latency, and a control group of relatives of these last patients, living in the same environmental conditions. House-dust mite allergen dosages revealed that the last two groups were exposed to at least 2  $\mu\text{g/g}$  of dust of *Der* group 1 (*Der p* I plus *Der f* I). Only conjunctival epithelial cells of patients allergic to mites mildly express ICAM-1, although completely symptom-free; these findings have been confirmed at nasal level (Ciprandi et al., submitted).

These experimental findings suggested some considerations to us. Firstly, in certain circumstances, clinical examination and symptoms are not sufficient to detect a pathologic process, since ICAM-1 expression on epithelial cells and the presence of inflammatory cells were detectable in the absence of any clinical sign. Secondly, ICAM-1 presence on epithelial cells may be considered to be a useful laboratory tool for monitoring allergic subjects exposed to allergen, and also clinical response to preventive and pharmacologic treatments. Finally, we thought that since subliminal (subclinical) exposure to the specific allergen can induce ICAM-1 expression, this effect might play a role in making allergic subjects more susceptible to rhinovirus infections (43, 47). At present, the viral infection has always been considered to be the primary effect leading to asthma symptoms in allergic subjects.

In the light of the ICAM-1 data on the minimal persistent inflammation in allergic disease and of the recent findings referred to above, we postulate that

ICAM-1 expression on epithelial cells may be regarded, at least in some cases of respiratory allergy, as a primary effect leading to asthma through the interaction virus, ICAM-1 having been previously induced by the allergen (Fig. 2). This hypothesis obviously has to be tested, but we believe this is a likely explanation of the strong effect of rhinovirus infection in asthmatic subjects.

### AM and allergic disease treatment

The recent advances in understanding of the critical role of AM in the pathogenesis of allergic inflammation have led to great interest in targeting these molecules as a new therapeutic approach. Wegner et al. (59) studied the use of an ICAM-1 monoclonal antibody (MAb) to prevent allergic inflammation and clinical symptoms. This same approach has been employed in rheumatoid arthritis patients, leading to transient improvement (36, 51).

However, therapy with MABs for widely expressed molecules, such as ICAM-1, cannot be more disease-specific than some currently available drugs, such as cyclosporin (49). Cyclosporin, in fact, has been reported to inhibit ICAM-1 synthesis by endothelial cells (49). Methotrexate, by increasing adenosine release, inhibits leukocyte adhesion mediated by CD11b/CD18 (18). Nonsteroidal antiinflammatory

drugs diminish neutrophil adhesion mediated by CD11b/CD18 (1), whereas corticosteroids, by inhibiting IL-1 production, diminish the expression of E-selectin and ICAM-1 by the stimulated endothelium. This may explain the diminished resistance to infections of patients treated with these agents (8, 19). Barnes (6) included cell adhesion blockers in the list of future antiinflammatory drugs for asthma treatment.

We investigated the possible effects of two compounds, deflazacort and cetirizine, on the previously described *in vivo* model of allergic inflammation, i.e., the allergen-specific conjunctival challenge. Deflazacort (DFZ), a new steroid compound, a prednisolone derivative, strongly inhibited the late-phase reaction processes, i.e., clinical variables, cellular inflammatory infiltrate, and ICAM-1 presence on conjunctival epithelial cells. Unexpectedly, DFZ partially blocked ICAM-1 expression in the early phase. This is the first experimental evidence that a systemic steroid inhibits an early-phase process of an allergic reaction (16). Cetirizine (CTR), a second-generation anti-H<sub>1</sub> compound, has a strong effect on all the clinical and cytologic variables caused by specific stimulation. We observed the CTR effect on both early and late phases (Ciprandi et al., submitted). However, a relevant conclusion can be drawn from this observation: ICAM-1 expression on epithelial cells is likely to be inhibited by CTR through a mechanism other than its anti-H<sub>1</sub> activity, since we found that histamine cannot induce ICAM-1 expression (17). These *in vivo* findings provide further insights into CTR "antiallergic" effects, since Kyan-Aung et al. (38) previously demonstrated that CTR, *in vitro*, inhibits adhesion of both eosinophils and neutrophils to the endothelium. Studies are presently in progress on the possible effects of other anti-H<sub>1</sub> drugs such as mizolastine, oxatomide, and terfenadine.

### Conclusion

The discovery and the functional studies of AM have provided new insights into many unsolved problems in immunology and cellular biology. An example of this concept is the finding, in 1987, of a "new" immunodeficiency, leukocyte adhesion deficiency (LAD), a recessive disease caused by a congenital defect of leukocyte LFA-1 expression (3). Very recently, at the end of 1992, a second form of LAD, called LAD II, has been described (28): a congenital defect in sialyl X expression is involved in this disorder. This is probably just the beginning of a "new era" in immunodeficiencies, since unknown congenital defects of other AM are likely to be discovered.

By analogy, new insights into understanding of

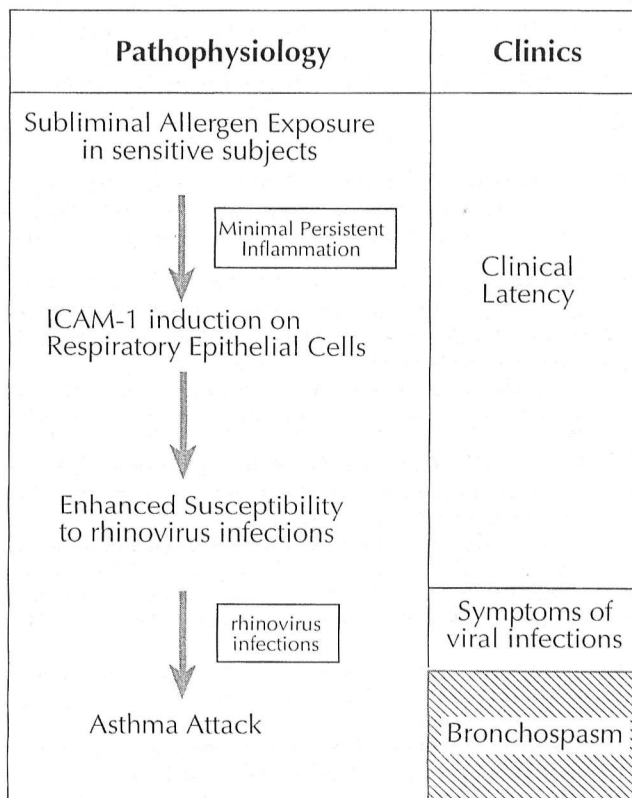


Fig. 2. Possible pathway of rhinovirus-induced asthma.

allergic inflammation have been promoted since 1990 by studies of AM involvement. Analysis of the possible functional roles of AM in the different stages and of the different cells of allergic inflammation have been reviewed, focusing also on the possible therapeutic perspectives. Much future work is needed to investigate these molecular aspects of allergic disorders.

Recent reports have revealed additional perspectives since Tanaka et al. (56) found that soluble AM (CD44) can bind the inflammatory cytokine MIP-1 $\beta$ . This phenomenon emphasizes the relevant role of soluble AM, since they should prolong the functional effects of proinflammatory cytokines, which in the soluble form have a very rapid lifetime in the site of inflammation (41).

All these findings further emphasize both the conception of inflammation as the major consequence of the allergic reaction and the basic concept that asthma is a "local" disease, as recently shown by a very interesting *in vivo* observation (41). At present, we believe that this notion should be extended to other allergic disorders, keeping in mind all the experimental evidence we reviewed here.

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