

Activated Leukocyte Cell Adhesion Molecule: A Novel Regulator of Allergic Inflammation in the Airways

Dendritic cells (DCs), the most proficient antigen-presenting cells of the immune system, are essential for the priming of immune responses (1). In the lungs, DCs are located at the basolateral site of the epithelium and continuously sense pathogens and other danger signals in the environment, traffic to the draining lymph nodes, and secrete cytokines, guiding the activation and differentiation of antigen-specific T cells (2). Seminal studies have uncovered DC-mediated T-cell priming as a prerequisite for the generation of T-helper cell type 2 (Th2) effector responses to inhaled allergens and for the development of allergic airway inflammation (3, 4).

The crosstalk between DCs and T cells is orchestrated by cognate interactions between receptors and ligands, organized in structures termed immunological synapses (5, 6). The formation of synapses is a highly dynamic process, involving the movement and spatial location of surface molecules (TCR [T-cell receptor]/MHC [major histocompatibility complex], CD28/B7, LFA-1 [lymphocyte function-associated antigen 1]/ICAM-1 [intercellular adhesion molecule 1], etc.), cytoskeleton proteins (F-actin and tubulin), and signal transduction molecules (tyrosine kinases, protein kinase B, etc.) (5, 6). Activated leukocyte cell adhesion molecule (ALCAM; also known as CD166) is expressed by several cell types, including neurons, fibroblasts, endothelial cells, and keratinocytes (7, 8), and exhibits critical biological functions, such as leukocyte extravasation, stabilization of the immunological synapse, T-cell activation, and tumor progression and metastasis (9–11). ALCAM has also pro-inflammatory functions in a model of delayed type hypersensitivity (12).

Expanding on these findings, in this issue of the *Journal*, Kim and colleagues (pp. 994–1008) investigate the *in vivo* role of ALCAM in two mouse models of allergic airway inflammation (ovalbumin [OVA]- and house dust mite-induced), using ALCAM^{-/-} mice (13). Initially, the authors demonstrate that ALCAM levels are increased in the BAL fluid and serum and decreased in the lung tissue in allergic mice compared with healthy controls. Notably, their findings revealed that ALCAM deficiency induced a significant amelioration in hallmarks of experimental asthma, including airway hyperresponsiveness, pulmonary inflammation, mucus secretion, and total numbers of infiltrating cells in the BAL fluid. In addition, allergen-specific Th2-cell responses in the periphery were significantly decreased, indicative of decreased T-cell activation in ALCAM^{-/-} mice compared with wild-type littermates. The results by Kim and colleagues are interesting and novel as they uncover a key role for ALCAM in allergic airway disease *in vivo*; still, several questions remain unanswered. For example, the current studies do

not distinguish between the *in vivo* effects of soluble versus cell-bound ALCAM. This is important, as soluble ALCAM (sALCAM) has been reported to negatively regulate ALCAM functions and to inhibit T-cell activation (8, 14). Nevertheless, considering that ALCAM^{-/-} mice, as well as *in vivo* depletion with an anti-ALCAM antibody, led to decreased allergen-driven airway inflammation, one can postulate that both sALCAM and cell-bound ALCAM have similar immune-stimulatory properties, and/or the effects of cell-bound ALCAM are predominant over those of the secreted form (Figure 1).

The authors went on to investigate the role of ALCAM in DC-mediated allergen priming *in vivo*. Their findings revealed that *in vivo* transfer of allergen-exposed bone marrow-derived DCs isolated from ALCAM^{-/-} mice into recipients whose CD4⁺ T cells bear a TCR that is specific for chicken OVA 323–339 peptide in the context of I-Ab, before OVA sensitization or challenge, resulted in decreased Th2 cell-associated inflammation, indicative of the inhibition of DC-induced T-cell priming. Still, examination of the immunophenotype of lung CD11c⁺CD11b⁺ DCs in ALCAM^{-/-} mice did not show discernible differences in the expression of the costimulatory molecules CD80, CD86, and CD40, suggesting that ALCAM deficiency affects other DC characteristics. Building on these results, it would be interesting to investigate whether ALCAM^{-/-} DCs acquire tolerogenic properties, such as expression of immunoregulatory molecules (PDL-1 [programmed death ligand 1], IDO [indoleamine 2,3-dioxygenase], IL-10, TGF-β [transforming growth factor-β], etc.), and drive the generation and/or expansion of T-regulatory (Treg) cells. Studies by our group and others have revealed that tolerogenic DCs hinder Th2 allergic responses and instruct Treg cells that restrain allergic airway inflammation upon transfer *in vivo* (2, 15). Taken together, one would expect that the amelioration of airway inflammation observed in ALCAM^{-/-} mice would be associated with increased numbers and/or function of Treg cells (Figure 1). Alternatively, as ALCAM participates in the formation of the immunological synapse, functional interactions between DCs and Treg cells may be altered in conditions wherein ALCAM is absent, leading to reduced Treg-cell responses. Future studies focusing on Treg cell-mediated responses in ALCAM^{-/-} mice should help resolve these important questions. Moreover, comprehensive analyses using high-throughput flow cytometry and molecular biology assays, including single-cell RNA sequencing, will provide critical insight into the effects of ALCAM signaling on DC phenotypic and functional characteristics.

Kim and colleagues also report that ALCAM deficiency decreases the trafficking of DCs and T cells in the airways, pointing

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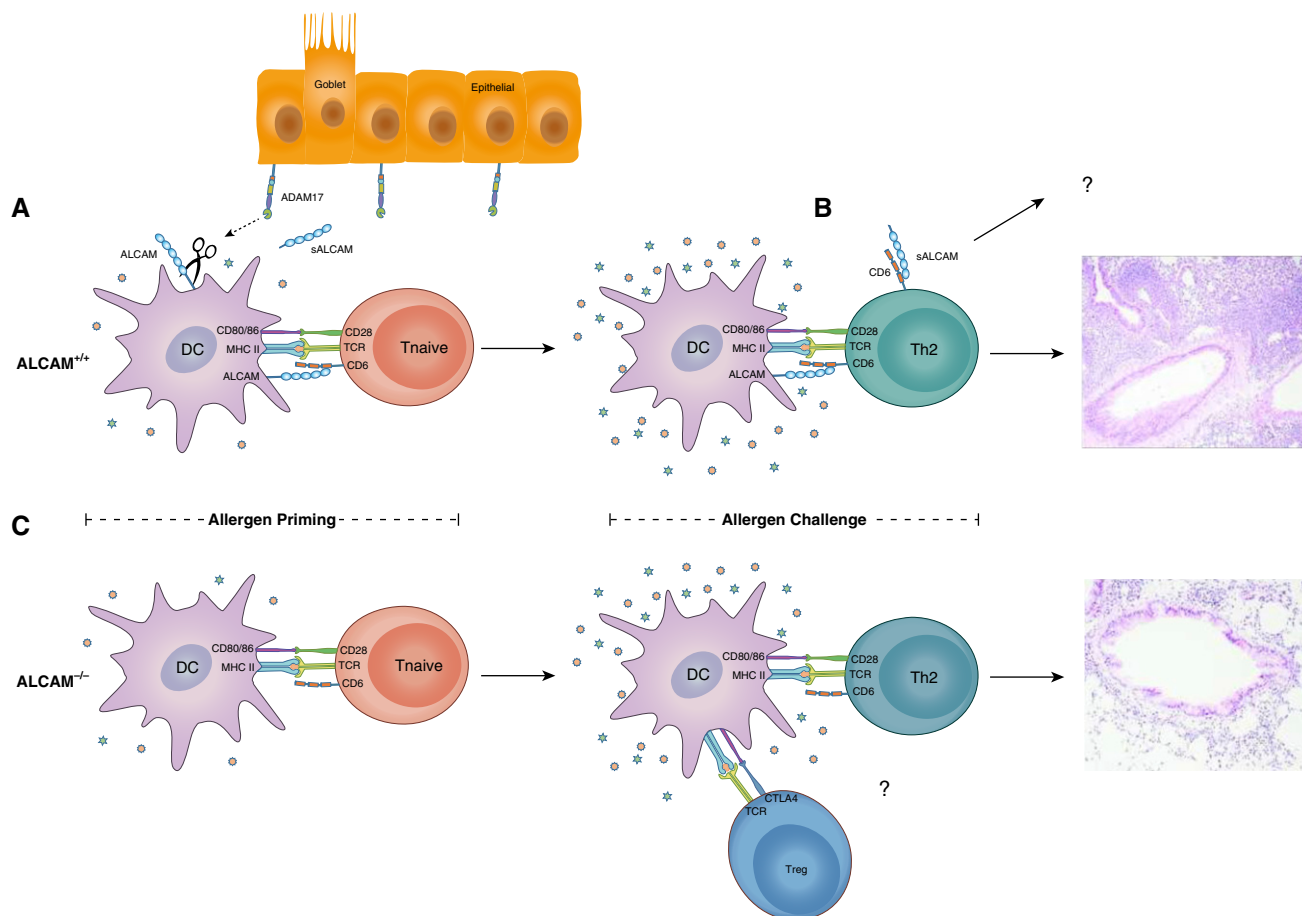


Figure 1. (A) Activated leukocyte cell adhesion molecule (ALCAM)^{+/+} dendritic cells (DCs), prime naive T cells in the presence of allergen, partly through the binding of ALCAM on DCs to CD6 on T cells. This leads to T-cell differentiation toward T-helper cell type 2 (Th2). On allergen challenge, ALCAM–CD6 interactions enhance Th2 effector responses, leading to the development of allergic airway inflammation. (B) In parallel, ADAM17 expression is elevated in lung tissue–resident cells and cleaves DC-bound ALCAM, releasing its soluble form (sALCAM). The outcome of the interactions of CD6 on the surface of Th2 cells with sALCAM remains elusive. (C) ALCAM^{-/-} DCs do not adequately prime T-cell responses, and thus, on allergen challenge, defective Th2 responses fail to induce allergic airway inflammation. ALCAM^{-/-} DCs may also promote the generation of regulatory T cells, suppressive against overactive allergic responses in the airways. Hematoxylin and eosin photos adapted from Reference 13. ADAM17 = a disintegrin and metalloproteinase 17; MHC II = major histocompatibility complex II; TCR = T-cell receptor; Naive = naive T cells; Treg = regulatory T cells.

to this as a mechanism underlying dampened airway inflammation. Additional investigation is, however, required to delineate the precise role of ALCAM in Th2-cell differentiation *in vivo*. Notably, in a therapeutic setting, the authors showed that *in vivo* administration of an ALCAM neutralizing antibody restrained clinical features of allergic airway inflammation, highlighting ALCAM as a potential new therapeutic target for allergic asthma. These findings, however, should be considered with caution. Given that ALCAM participates in fundamental biological processes, including T-cell activation (10, 11), a key question that arises is how ALCAM signaling can be inhibited *in vivo* without inducing overt immune suppression, leading to serious complications, such as chronic infections and/or cancer. In fact, decreased ALCAM levels have been linked to malignancy and poor prognosis in patients with breast cancer (16, 17). In this context, administration of anti-ALCAM antibody and/or inhibitors locally in the affected airways may provide

significant therapeutic benefit and should be investigated in future studies.

In line with the data on the mouse experimental models, Kim and colleagues discovered increased ALCAM levels in the serum and sputum in children with asthma. In addition, they identified an ALCAM variant that confers protection against asthmatic disease. Although these findings seem very promising, it is too soon to suggest ALCAM as a novel biomarker for allergic asthma. The challenge now is to validate these findings in a larger cohort of patients, including adults, and to consolidate the significance of the ALCAM variant in disease protection. In closing, Kim and colleagues have conducted an ambitious and well-designed study that constitutes an important contribution to our current knowledge of the role of ALCAM in DC–Th2-cell interactions with potentially important ramifications for human asthma. ■

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References

1. Mildner A, Jung S. Development and function of dendritic cell subsets. *Immunity* 2014;40:642–656.
2. Deckers J, De Bosscher K, Lambrecht BN, Hammad H. Interplay between barrier epithelial cells and dendritic cells in allergic sensitization through the lung and the skin. *Immunol Rev* 2017;278:131–144.
3. Plantinga M, Guillems M, Vanheerswyngheels M, Deswarte K, Branco-Madeira F, Toussaint W, et al. Conventional and monocyte-derived CD11b(+) dendritic cells initiate and maintain T helper 2 cell-mediated immunity to house dust mite allergen. *Immunity* 2013;38:322–335.
4. Xanthou G, Alissafi T, Semitekolou M, Simoes DC, Economidou E, Gaga M, et al. Osteopontin has a crucial role in allergic airway disease through regulation of dendritic cell subsets. *Nat Med* 2007;13:570–578.
5. Felix NJ, Suri A, Salter-Cid L, Nadler SG, Gujrathi S, Corbo M, et al. Targeting lymphocyte co-stimulation: from bench to bedside. *Autoimmunity* 2010;43:514–525.
6. Rothoef T, Balkow S, Krummen M, Beissert S, Varga G, Loser K, et al. Structure and duration of contact between dendritic cells and T cells are controlled by T cell activation state. *Eur J Immunol* 2006;36:3105–3117.
7. Giunta M, Favre A, Ramarli D, Grossi CE, Corte G. A novel integrin involved in thymocyte-thymic epithelial cell interactions. *J Exp Med* 1991;173:1537–1548.
8. Ikeda K, Quertermous T. Molecular isolation and characterization of a soluble isoform of activated leukocyte cell adhesion molecule that modulates endothelial cell function. *J Biol Chem* 2004;279:55315–55323.
9. Zimmerman AW, Joosten B, Torensma R, Parnes JR, van Leeuwen FN, Figdor CG. Long-term engagement of CD6 and ALCAM is essential for T-cell proliferation induced by dendritic cells. *Blood* 2006;107:3212–3220.
10. Iolyeva M, Karaman S, Willrodt AH, Weingartner S, Vigl B, Halin C. Novel role for ALCAM in lymphatic network formation and function. *FASEB J* 2013;27:978–990.
11. Santos RF, Oliveira L, Carmo AM. Tuning T cell activation: the function of CD6 at the immunological synapse and in T cell responses. *Curr Drug Targets* 2016;17:630–639.
12. von Bauer R, Oikonomou D, Sulaj A, Mohammed S, Hotz-Wagenblatt A, Gröne HJ, et al. CD166/ALCAM mediates proinflammatory effects of S100B in delayed type hypersensitivity. *J Immunol* 2013;191:369–377.
13. Kim MN, Hong JY, Shim DH, Sol IS, Kim YS, Lee JH, et al. Activated leukocyte cell adhesion molecule stimulates the T-cell response in allergic asthma. *Am J Respir Crit Care Med* 2018;197:994–1008.
14. Bowen MA, Aruffo AA, Bajorath J. Cell surface receptors and their ligands: in vitro analysis of CD6-CD166 interactions. *Proteins* 2000;40:420–428.
15. Semitekolou M, Morianos I, Banos A, Konstantopoulos D, Adamou-Tzani M, Sparwasser T, Xanthou G. Dendritic cells conditioned by activin A-induced regulatory T cells exhibit enhanced tolerogenic properties and protect against experimental asthma. *J Allergy Clin Immunol* 2018;141:671–684.
16. Mezzananza D, Fabbi M, Bagnoli M, Staurengo S, Losa M, Balladore E, et al. Subcellular localization of activated leukocyte cell adhesion molecule is a molecular predictor of survival in ovarian carcinoma patients. *Clin Cancer Res* 2008;14:1726–1733.
17. Burandt E, Bari Noubat T, Lebeau A, Minner S, Burdelski C, Jänicke F, et al. Loss of ALCAM expression is linked to adverse phenotype and poor prognosis in breast cancer: a TMA-based immunohistochemical study on 2,197 breast cancer patients. *Oncol Rep* 2014;32:2628–2634.

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How Long Should We Be Vigilant after a Hospitalization for a Chronic Obstructive Pulmonary Disease Exacerbation?

The prognosis after a hospitalization for a chronic obstructive pulmonary disease (COPD) exacerbation is of substantial interest to patients, caregivers, clinicians, policymakers, and other stakeholders. In the United States, the mean 30-day all-cause risk of readmission after a hospitalization for a COPD exacerbation is about 20%, but the risk can vary between 17% and 28% across different hospitals (1). Likewise, the risk for death after a hospitalization for a COPD exacerbation is about 9% at 30 days, but can vary between 6% and 14% (2). Multiple factors contribute to the variability in the 30-day risks for readmissions and death, including the need for ventilatory support for respiratory failure, use of home oxygen, presence of coexisting conditions, patient's social support and other socioeconomic factors, patient self-management skills and behaviors, quality of inpatient care, and accessibility to high-quality postdischarge care (3–7). In response to these observations in the United States and similar findings in other countries, policymakers

have sought to reduce the short-term risk for adverse outcomes by promoting the delivery of transitional care services tailored to the populations that hospitals serve (8, 9).

Some studies have also examined the longer-term risks of a readmission and death after a hospitalization for a COPD exacerbation. Five studies in Europe (100–757 patients per study in the Netherlands, Spain, and United Kingdom) suggest that the all-cause risk for death at 1 year is 22–36%, or at least double the risk observed at 30 days (10–14). The corresponding risks of 1-year outcomes in the United States, however, are not as well understood. In this issue of the *Journal*, Lindenauer and colleagues (pp. 1009–1017) fill this important knowledge gap (15). Lindenauer and colleagues analyzed the risks of all-cause readmission and death after more than 2.3 million hospitalizations among U.S. Medicare beneficiaries who were at least 65 years old and compared their findings with age-, sex-, and race-adjusted risks in a general population of more than 23 million U.S. Medicare beneficiaries.

There are several notable findings. First, the 1-year cumulative risks of readmission and death after a hospitalization for a COPD

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