



fied mice with minimal or no steady-state phenotype. In many ways these mice could be viewed as models for otherwise normal adult humans who exhibit exaggerated or unexpected responses to inflammation, infectious agents, or cancer progression. As such, they have the potential to identify and dissect regulatory pathways that influence but do not cause disease.

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An unexpected role for the anaphylatoxin C5a receptor in allergic sensitization

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The anaphylatoxins complement component 3a and 5a (C3a and C5a, respectively) are classically seen as proinflammatory mediators of allergic asthma that recruit inflammatory cells, induce edema, and cause bronchoconstriction. A few years ago, controversy arose when it was shown that C5-deficient mice were more susceptible to experimental asthma compared with C5-sufficient mice. In a study by Köhl et al. in this issue of the JCI, it is shown in a series of truly “complementary” experiments that C5a receptor (C5aR) blockade promotes Th2 sensitization upon first exposure to inhaled allergen, whereas C5aR blockade during established inflammation suppresses the cardinal features of asthma (see the related article beginning on page 783). Blockade of C5aR alters the function of airway DCs, crucial for inducing and maintaining Th2 responses in the lung. Targeting C5aR as a treatment for established asthma could be beneficial, but might be accompanied by sensitization to novel antigens.

Allergy is mediated by Th2 cells

The incidence of allergic diseases is currently on the rise. In western societies, up to 25% of children are sensitized to allergens such as the house dust mite (HDM), pollen, animal dander, or food

components. This sensitization is indicated clinically by the presence in the serum of allergen-specific IgE and by an immediate wheal and flare reaction after skin prick testing with these allergens. In most, but not all, sensitized individuals, natural allergen exposure via food or inhalation can lead to allergic diseases such as allergic asthma, allergic rhinitis, or atopic dermatitis. These diseases have an inflammatory component characterized by edema, plasma extravasation, accumulation of eosinophils and mast cells, and overproduction of mucus (1, 2). In the case of allergic asthma, an additional symptom

is airway hyperresponsiveness (AHR) to all kinds of specific and nonspecific stimuli, which is caused by excessive smooth muscle contraction, resulting in airway narrowing. Allergic sensitization is the result of an aberrant Th2 response to allergens. Th2 lymphocytes produce cytokines that control Ig-class switching toward IgE production (e.g., IL-4), allergic eosinophilic inflammation (e.g., IL-5), and AHR (e.g., IL-9, IL-13). In support of a critical role for Th2 cells, experimental asthma does not develop in mice deficient in CD4 cells or most of the above cytokines (3).

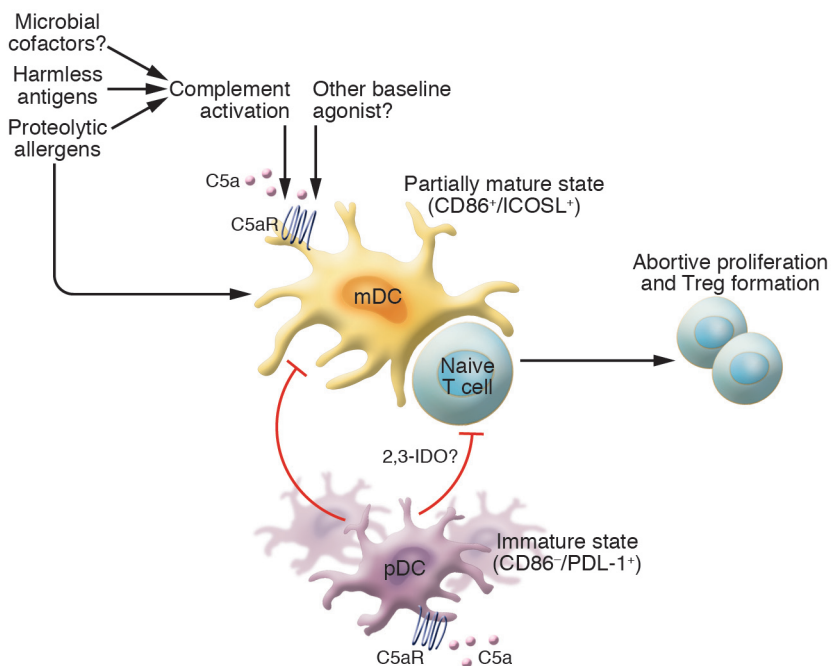
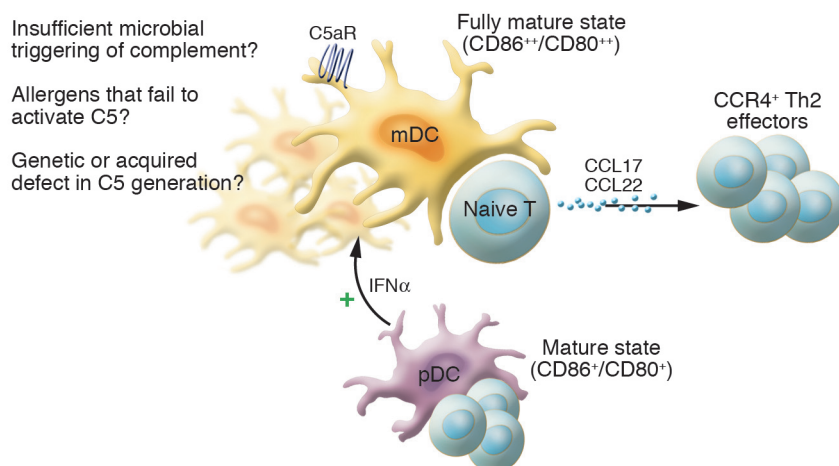
The complement system in asthma

The complement system is crucial for innate host defense because of its formation of a lytic effector system that protects against pathogens. Serine proteases generated in response to classical and alternative activation of complement can cleave the anaphylatoxic peptides complement 3a (C3a) and C5a from C3 and C5, respectively (4). Various components of the complement pathway have been implicated in mediating allergic inflammation (5, 6). First, the anaphylatoxins C3a and C5a are found in increasing concentrations in the bronchoalveolar lavage fluid of asthmatic

Nonstandard abbreviations used: AHR, airway hyperresponsiveness; C3a, complement component 3a; C5aR, C5a receptor; CCL17, CC chemokine ligand 17; CCR4, CC chemokine receptor 4; HDM, house dust mite; mDC, myeloid DC; pDC, plasmacytoid DC.

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**A Tolerance to inhaled allergens****B Sensitization to inhaled allergens****Figure 1**

Immune regulation by DC subsets and the influence of complement. **(A)** Under conditions of immune tolerance to inhaled antigens, pDCs outnumber mDCs. pDCs suppress the generation of effector cells by mDCs by sending an unknown inhibitory signal to mDCs and to T cells (in the form of programmed death ligand-1 [PDL-1] or high level indoleamine dioxygenase [2,3-IDO] activity). The T cell division that occurs in response to partially mature mDCs is abortive (i.e., it does not lead to generation of effector cells) and leads to generation of Tregs. ICOSL, inducible costimulator ligand. **(B)** Under conditions that lead to sensitization to inhaled antigens, mature mDCs greatly outnumber pDCs, thus releasing the inhibitory “brake” on T cell stimulation. It is also possible that pDCs become directly stimulatory, subsequently inducing rather than suppressing T cell responses. In this issue of the *JCI*, Köhl et al. (15) show that, under conditions of C5aR blockade or lack of C5 generation, there is a major increase in the number of mDCs compared with pDCs, leading to the Th2 sensitization. mDCs also produce the Th2-selective chemokines CCL17 and CCL22, further intensifying Th2 effector cytokine production. This might explain why C5-deficient mice are more susceptible to asthma. Exactly how complement is activated in response to allergen inhalation is still unknown, but could involve exposure to proteolytic allergens, production of endotoxin by microbes, or baseline activation in the lungs. If microbial factors induce C5a in the lungs, the absence of these might also explain an increase in sensitization with increased cleanliness (hygiene hypothesis).

ics and mice with experimentally induced asthma, compared with controls (7–9). Second, these components can induce smooth muscle contraction, mucus secretion, increased microvascular permeability, leukocyte migration and activation, and degranulation of some types of mast cells, thus mimicking some essential features of asthma (10). Third, and most important, neutralization of anaphylatoxin activity through the use of blocking antibodies or genetic targeting of various complement factors or their receptors has been shown to attenuate allergic inflammation and AHR in mice and guinea pigs (7, 11–13). A few years ago, it therefore

came as somewhat of a surprise that A/J mice, a particular mouse strain in which it is very easy to induce allergic inflammation and AHR, were deficient in C5, whereas C3H/HeJ mice with normal levels of C5 were resistant to OVA-induced experimental asthma (14, 15).

In this issue of the *JCI*, Köhl et al. provide an explanation for this apparent “C5a paradox” (15). The authors developed 3 truly “complementary” models to address the role of C5a in asthma. Rather than deleting C5a, they blocked 1 of its 2 receptors, the 7 transmembrane protein C5a receptor (C5aR; also known as CD88). To block C5aR, they used either (a) an anti-C5aR

mAb administered to the lungs; (b) a lung-inducible mutant form of C5a (C5aRA A8^{A71-73}) that acts as a C5aR antagonist; or (c) C5aR-deficient mice. When naive mice received OVA via inhalation in the absence of systemic adjuvant, tolerance was the outcome (16–18), but when the C5aR was blocked, Th2 sensitization occurred and mice mounted a serum IgE response to OVA, produced Th2 cytokines, and developed florid peribronchial inflammation leading to AHR. The weak Th2 response that occurs in naive mice in response to inhalation of the natural allergen HDM was also greatly enhanced during C5aR blockade. However, when C5aR was blocked during



airway allergen challenge in already Th2-sensitized mice, allergic inflammation was attenuated. It seems therefore that the effects of complement activation are different during allergen sensitization compared with those effects observed once inflammation is established, which might explain why C5 neutralization had paradoxical effects in various models of asthma.

Th2-type allergic sensitization is controlled by DCs

The explanation as to why complement activation protects against allergic sensitization is more complex, but this process involves alterations in the function of antigen-presenting DCs (19, 20). These cells form a network in the upper layers of the epithelium and lamina propria of the airways, gut, and skin. Here, DCs are said to be in an immature state, specialized for internalizing foreign antigens but not yet able to activate naive T cells. Upon recognition of antigen in the context of a danger signal (pathogen- or damage-associated molecular patterns), DCs migrate to the draining lymph nodes on their way, processing the antigen into the MHC complex. In the lymph nodes, they become fully mature and provide costimulatory molecules and cytokine signals for initiating and polarizing the T helper response (21, 22). Several groups have demonstrated that respiratory tract myeloid DCs (mDCs) are prone to inducing Th2 responses in the airways by default (23). They produce little IL-12, a prototype Th1-skewing cytokine, yet secrete the Th2-prone cytokine IL-6 (24, 25). Not surprisingly, airway DCs have been closely implicated in the process of allergic sensitization. Adoptive transfer of cultured mDCs pulsed with allergens is able to induce Th2 sensitization (26). Conversely, allergic airway inflammation does not develop in mice depleted of DCs (27).

As most allergens are immunologically inert proteins, the usual outcome of their inhalation is immune tolerance, and inflammation does not develop upon chronic exposure (16, 18). It was therefore long enigmatic how sensitization to allergens occurred. An important discovery was the fact that most clinically important allergens, such as the major Der p 1 allergen from HDM, are proteolytic enzymes that can directly activate DCs or epithelial cells to break the process of tolerance and promote Th2 responses (28, 29). However, other allergens, such as the experimental allergen OVA, do not have

any intrinsic activating properties. For these antigens, contaminating molecules or environmental exposures (e.g., respiratory viruses and air pollution) might “pull the trigger” for DC activation. Eisenbarth et al. very elegantly showed that signals from the innate immune system, such as activation of the TLR system by endotoxin, break inhalational tolerance to OVA, with low doses of endotoxin promoting Th2 responses and high doses promoting Th1 responses through modification of DC maturation and cytokine production (30). This is clinically important as most natural allergens, such as HDM, cockroach, and animal dander contain endotoxin and undoubtedly other TLR agonists (31).

DC subset specialization in the lung

From the data discussed above, it seems that the ability of the pulmonary immune response to mount either a tolerogenic or immunogenic response is controlled by the maturation state of mDCs interacting with naive T cells, a process driven by signals from the innate immune system (3, 32). Immature or partially mature mDCs expressing inducible costimulator ligand induce abortive T cell proliferation in responding T cells and the formation of Tregs, whereas fully mature mDCs induce Th1 or Th2 immunity (17, 18, 33). Complexity arose when we and others demonstrated that respiratory tolerance might be a function of a subset of plasmacytoid DCs (pDCs) (16, 34). In humans, pDCs were described in the bloodstream, lungs, and lymph nodes as lineage^{neg} CD11c^{lo}CD123⁺B220⁺ cells (35). In the mouse, pDCs express specific markers (e.g., 120G8 and PDCA-1) as well as cell markers shared with mDCs (e.g., MHCI, MHCII, and CD11c) but also with granulocytes (e.g., Gr1) and B cells (e.g., B220) (35). This cellular subset is known for its massive production of type I IFN upon viral infection and for its potential to differentiate into mature APCs upon proper TLR stimulation (36). Unexpectedly, it was found that removal of pDCs from mice, using depleting antibodies, led to a break in inhalational tolerance to OVA and to development of asthmatic inflammation (16). The precise mechanisms by which pDCs promote tolerance are unknown, but in the absence of pDCs, mDCs become more immunogenic and induce the formation of effector cytokines from dividing T cells (Figure

1) (32). Ex vivo, lung-derived pDCs also promoted formation of Treg cells specific for OVA (16).

Complement C5aR controls DC function in the airways

In the article by Köhl et al. in this issue (15), it is again shown that lung mDCs are the predominant cell type that induces effector cytokine production by CD4⁺ T cells, whereas pDCs do not stimulate effector cytokine production and even directly inhibit mDC-driven T cell activation (Figure 1) (15). Blockade of the C5aR during priming to inhaled OVA or HDM led to development of an effector Th2 response, which might signify a break in inhalational tolerance or an enhancement of an already weak Th2 response. In any case, exposure to the natural allergen HDM led to an early (within 16 hours) and persistent increase in the number of immunogenic mDCs whereas the number of tolerogenic pDCs was unaffected. When C5aR was blocked, the relative increase in the number of mDCs was even higher, approaching 100 mDCs to 1 pDC. Under these conditions of low pDC numbers, a break in inhalational tolerance occurs (16). However, C5aR blockade might also lead to enhanced Th2 polarization, which already occurs by default in the airways (23). C5a has been shown to induce Th1 responses by its ability to enhance IL-12 production in APCs (14). It is unknown whether C5aR blockade leads to an enhancement of Th2 priming by a lack of counterbalancing IL-12 production by APCs. An experiment using IL-12 administration could have answered this question. It has also been shown that C5a can interfere with TLR4 signaling — C5aR activation negatively impacts IL-12, IL-23, and IL-27 production (37). In view of the modulating effects of endotoxin exposure on Th2 sensitization in the airways, this needs to be further explored (30).

Under in vitro Th2 polarizing conditions, as well as in Th2-mediated diseases, lymphocytes express CC chemokine receptor 4 (CCR4) and CCR8 (38). It is well known that DCs are a predominant source of chemokines for naive T and B cells, but they are similarly able to produce chemokines that attract effector T cells (21). Upon C5aR blockade, mDCs produce large amounts of CC chemokine ligand 17 (CCL17, a thymus and activation-regulated chemokine) and CCL22 (a macrophage-derived chemokine), the



known ligands for CCR4. In this way, mDCs might cause a more effective Th2 response in the lungs and a higher recruitment of Th2 cells into inflamed airways, which would explain the higher effector Th2 cytokine production levels in C5aR-targeted mice. Again, this might be clinically relevant information. Hammad et al. have described the production of CCL17 and CCL22 by human monocyte-derived DCs in response to Der p 1 recognition, preferentially in mDCs derived from HDM-allergic donors, whereas in non-HDM-allergic healthy controls Der p 1 induced mainly CxCL10 (39). The precise role of complement activation was not addressed, but Der p 1 might liberate C5a from C5 due to the cysteine protease activity of Der p 1, preferentially in individuals allergic to HDM.

Prospects for the future

The Köhl et al. study (15) raises many questions for future research. It illustrates how the fine-tuning of DC function by signals from the allergen and the innate immune response is crucial to understanding the process of allergic sensitization (Figure 1). In this regard, it will be paramount to understand how mDCs react to natural allergens, how pDCs influence mDC function, and precisely how complement activation alters these processes. It has not been addressed whether C5aR triggering interferes with the development or function of Tregs, which are closely involved in respiratory tolerance (17, 18, 40). The same group of authors, headed by Marsha Wills-Karp, have recently shown that in the C5-sufficient strain of C3H/HeJ mice, Tregs function to suppress inflammation by downregulating DC function, whereas in C5-deficient mice they fail to do so (41).

To proceed, we need more precise information regarding if and how complement is activated in response to inhalation of harmless proteins or natural allergens (7). In this regard, DCs can themselves be a source of complement proteins and cascade activation and regulation (42). The role of concomitant microbial factors needs further clarification, as a lack of these might lead to less complement activation and thus to increased sensitization, possibly explaining the hygiene hypothesis of increased allergy. We need to study whether there are genetic polymorphisms underlying the efficiency by which C5a is generated or in C5aR structure and function, as these might be risk

factors for developing Th2 sensitization or more severe inflammation in response to allergen inhalation. As this study only utilizes antagonism of the C5aR, it is not formally proven whether C5a itself — or some structurally related molecule — is inhibiting allergic sensitization. Another aspect that needs further attention is the role of the second C5a receptor, C5L2. Because this receptor interferes with the function of the classical C5aR, it is possible that high level expression on DCs also confers a risk of becoming Th2 sensitized (43).

Finally, C5aR antagonists might be of therapeutic benefit for the treatment of established asthma. In view of the current findings, however, one will need to carefully monitor the occurrence of novel Th2 sensitizations. The Th2-inducing potential of C5aR antagonists might be harmful in the long-term and may possibly induce progression of the disease.

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Good news in the nuclear envelope: loss of lamin A might be a gain

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Genetic diseases often reveal the physiological roles of the affected proteins. The identification of mutations in the nuclear envelope proteins lamin A and lamin C as the cause of a diverse group of human diseases has expanded our understanding of the lamin proteins from being merely structural elements of the cell nucleus and has implicated them in novel cellular functions including signal transduction and gene expression. However, it now appears that the physiological relevance of one of the lamin proteins in organismal function has been overestimated. In this issue of the *JCI*, Fong et al. demonstrate that lamin A-deficient mice are phenotypically normal (see the related article beginning on page 743). The good news is these findings open the door to a new strategy for the therapeutic treatment of diseases caused by mutations in lamin A, such as muscular dystrophies and some types of premature aging syndromes.

Laminopathies are genetic diseases caused by mutations in the *LMNA* gene, which encodes lamins A and C (1). This diverse group of diseases includes several types of muscular dystrophies, lipodystrophies, and, curiously, premature aging diseases. One of the intriguing aspects of these diseases is that the affected gene encodes 2 of the most widely expressed structural proteins of the cell nucleus. Lamins A and C are intermediate filament-type proteins that, together with B-type lamins, form an extensive polymer network at the nuclear periphery (1). This nuclear lamina was long considered a merely passive

support structure for the cell nucleus but is now recognized as far more multifunctional and contributing to transduction of mechanical forces to the nucleus and to gene regulation via tethering of genes to the nuclear periphery. In addition, the lamins are also present in the nuclear interior, where they have been implicated in organizing transcription, replication, and DNA repair (2).

No targeted therapies are available for laminopathies, and their molecular basis is poorly understood. One of the complications in analyzing lamin function is that lamins A and C are generated from the same gene, *LMNA*, by alternative splicing (3) (Figure 1A). Mature lamin A differs from lamin C by a 74-aa C-terminal addition and is generated from a precursor prelamin A protein. Prelamin A then undergoes extensive posttranslational processing, during which its C terminus

is modified by farnesylation, followed by endoproteolytic cleavage by the Zmpste24 protease (FACE1 in humans) (4). This farnesylation appears to be crucial since it promotes targeting of the lamin A protein to the nuclear periphery (5). Partially due to this elaborate processing mechanism, lamin A has long been considered the more important of the 2 isoforms, with lamin C merely playing a subordinate, auxiliary role. This view was recently reinforced by the discovery that mutations in *LMNA* that affect only lamin A, but not lamin C, led to accumulation of the farnesylated prelamin A intermediate, which acts in a dominant fashion to cause the premature aging disorder Hutchinson-Gilford progeria syndrome (HGPS) (6, 7). In this issue of the *JCI*, Fong et al. now directly challenge the notion of the paramount importance of lamin A by demonstrating that gene-targeted mice possessing only lamin C, but no lamin A or prelamin A, are indistinguishable from wild-type mice (8).

A lamin C-only mouse

Fong et al. (8) generated “lamin C-only” mice (*Lmna*^{LCO/LCO}) by creating a mutant *Lmna* allele that does not produce a prelamin A transcript. Based on growth rate, life span, bone structure, and muscle functionality, *Lmna*^{LCO/LCO} mice appeared indistinguishable from wild-type mice, and histopathological analysis did not reveal any tissue abnormality. This is in

Nonstandard abbreviations used: FTI, farnesyltransferase inhibitor; HGPS, Hutchinson-Gilford progeria syndrome.

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