

Driving IL-17⁺ $\gamma\delta$ T-cell migration in allergic reactions: A new “inflammatory” role for the “homeostatic” chemokine CCL25

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Chemokines are traditionally classified as homeostatic or inflammatory depending on whether they direct leukocyte migration in the absence or presence of inflammatory stimuli. CC chemokine ligand (CCL)25, a ligand for CC chemokine receptor (CCR)9, has mostly been characterized as a homeostatic chemokine that determines the migration pathway of T-cell progenitors within the thymus, and the recruitment of various lymphocyte subsets to the intestinal mucosa. In this issue of the *European Journal of Immunology*, Costa et al. [Eur. J. Immunol. 2012. 42: 1250–1260] describe a new inflammatory role for CCL25/CCR9 in controlling the migration of a subset of $\gamma\delta$ T cells committed to IL-17 production ($\gamma\delta$ 17 cells) in a model of allergic pleurisy. Interestingly, the effect of CCL25 was selective for $\gamma\delta$ 17 cells, as it did not extend to other $\gamma\delta$ or $\alpha\beta$ T-cell subsets, and resulted in a specific increase of IL-17 (but not IL-4 or IFN- γ) levels in the allergic pleura. In this commentary, I discuss these results in the context of chemokine-mediated recruitment of $\gamma\delta$ T cells to inflammatory sites, and the as yet unclear and controversial role of IL-17 in allergic reactions.

Keywords: Allergy • Chemokines • IL-17 • Inflammation • $\gamma\delta$ T cells



See accompanying article by Costa et al.

One of the key characteristics of $\gamma\delta$ T cells is their abundance in peripheral tissues. Thus, murine $\gamma\delta$ T cells typically constitute less than 2% of the T-cell pool present in secondary lymphoid organs (lymph nodes, spleen), but account for approximately 50% (small intestine) up to 95% (skin) of the respective intra-epithelial lymphocyte (IEL) compartments [1]. The establishment of these $\gamma\delta$ IEL populations occurs very early in ontogeny (late embryo or newborn) and depends on $\gamma\delta$ T-cell migration from the thymus to the peripheral tissues. This process is orchestrated by particular chemokines and their receptors: namely, skin homing is controlled by CC chemokine ligand (CCL)27/ CC chemokine receptor (CCR)10, whereas, gut homing is directed by CCL25/ CCR9 [2] (Fig. 1).

Chemokines, such as CCL27 and CCL25, that coordinate leukocyte trafficking during tissue development and maintenance (under steady-state) are termed “homeostatic.” These contrast with “inflammatory” chemokines, which are induced during immune responses and recruit leukocytes to the sites of inflammation (triggered by the host reaction to infectious microorganisms or allergens, for example). In the case of $\gamma\delta$ T cells, Penido et al. had previously shown that CCL2 (the ligand for CCR2) played such a role by attracting substantial numbers of lymphoid $\gamma\delta$ T cells to sites of infection [3] and allergic inflammation [4]. In this issue of the *European Journal of Immunology*, a further paper from this group [5] now shows that “homeostatic” CCL25 is also important in a model of allergic pleurisy through recruitment of a subset of $\gamma\delta$ T cells specialized in the production of interleukin-17 (IL-17).

IL-17-producing $\gamma\delta$ ($\gamma\delta$ 17) cells have recently emerged as key players in immune responses to infection and tumors, as well as in autoimmunity [6–9]. $\gamma\delta$ 17 cells are generated in the thymus

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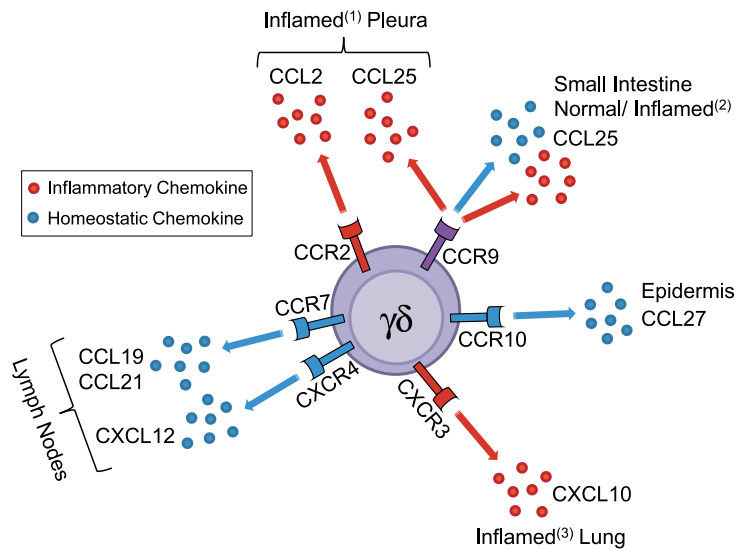


Figure 1. Homeostatic and inflammatory roles of chemokines in $\gamma\delta$ T-cell migration. The figure shows a number of chemokines and their receptors that play important roles in $\gamma\delta$ T-cell migration under homeostatic (in blue) or inflammatory (in red) conditions and the tissues to which the cells migrate to. “Inflamed” relates, for example, to the effects of (A) allergens or microbial (*Mycobacterium*) antigens; (B) Crohn’s disease or ileitis; (C) microbial (*Mycobacterium tuberculosis*) infection. Chemokine receptors display a 7-transmembrane structure that has not been depicted for simplicity.

starting already in the embryonic stages [10,11] and are contained within the CD27⁺ compartment of $\gamma\delta$ T cells, both in the thymus and in the periphery [10]. Peripheral $\gamma\delta$ T cells respond very rapidly to challenge, as tested in murine models of infection [12] and autoimmunity [8]. In both cases, $\gamma\delta 17$ cell expansion seems to be highly dependent on innate inflammatory stimuli, such as IL-1 β and IL-23 [8,12]. Interestingly, the chemokine receptor CCR6 has been shown to constitute a selective marker for murine $\gamma\delta 17$ cells [13], and more generally for IL-17⁺ T cells in humans [14].

While considerable mechanistic insight into $\gamma\delta 17$ cell development (in the thymus) and expansion (in peripheral lymphoid organs) has been gained, we still know very little about recruitment of these cells to inflammatory sites. In their new report, Costa et al. [5] provide strong evidence for the migration of $\gamma\delta 17$ cells (expressing CCR9) in response to the intra-pleural accumulation of CCL25 following OVA challenge. They observed $\gamma\delta 17$ cell recruitment both in the allergic pleurisy model and upon intra-pleural injection of purified CCL25. Conversely, anti-CCL25 antibody treatment inhibited $\gamma\delta 17$ cell migration into the allergic pleura. Importantly, this effect was specific to the $\gamma\delta 17$ subset, since both $\alpha\beta$ T cells and the remaining IL-17⁺ $\gamma\delta$ T cells were still recruited despite CCL25 neutralization. Consistent with this, the exogenous provision of CCL25 attracted $\gamma\delta 17$ cells but not IFN- γ ⁺ or IL-4⁺ $\gamma\delta$ T cells, and this was associated with a selective increase in IL-17 levels in the mouse pleura [5].

In this commentary, I discuss three topics that contextualize the new findings by Costa et al. [5]: first, the homeostatic versus inflammatory functions of CCL25; second, the migration of $\gamma\delta$ T cells to sites of inflammation; and, third, the potential roles of IL-17 (and $\gamma\delta 17$ cells) in allergic reactions.

CCL25-dependent T-cell migration in homeostatic versus inflammatory conditions

CCL25, also known as thymus-expressed chemokine (TECK), controls the migration of CCR9⁺ T-cell precursors to and within the

thymus, and thus is important at early stages of T-cell development. The CCL25/CCR9 axis seems to work synergistically with CCL21/CCR7, and the genetic ablation of both chemokine receptors leads to impaired development of the first “ $\gamma\delta$ T-cell wave” in mouse ontogeny (at embryonic day 15–17 of gestation) [15], a subset that populates the epidermis with invariant V γ 5V δ 1 T cells. These cells are also known as “dendritic epidermal T cells” and constitute an important first line of defense against injury or transformation [1,6].

Interestingly, although the migration of V γ 5V δ 1 T cells from the thymus to the skin does not depend on CCR9, but rather CCR10 (Fig. 1), the main “tissue address” conferred by CCR9 expression is actually the small intestine, where the epithelium produces large amounts of CCL25. An important study by Svensson et al. showed that CCL25 neutralization prevented the recruitment of effector T lymphocytes to the small intestinal epithelium [16]. However, CCR9-deficient animals displayed a specific impairment in $\gamma\delta$, but not $\alpha\beta$, IEL numbers [17,18], suggesting a lack of alternative (compensatory) mechanisms to CCL25/CCR9-dependent migration of $\gamma\delta$ T cells during gut homing.

While the role of CCL25 as a homeostatic chemokine is undisputed, various reports have unraveled its involvement in gut inflammation. In inflammatory bowel diseases, such as Crohn’s disease, CCL25 is expressed in aberrant patterns, which are associated with the altered distribution of CCR9⁺ lymphocytes with regard to the small intestine, the colon, and the blood [19,20]. Furthermore, the neutralization of CCL25 has been shown to ameliorate inflammation in early stages of a murine model of ileitis [21].

The report by Costa et al. [5] discloses a new inflammatory function for CCL25 outside the gut. In the pleura, which is a nonmucosal tissue, CCL25 can also be produced by epithelial (mesothelial) cells upon OVA challenge in vivo (or IL-4 treatment in vitro) [5]. This then triggers the recruitment of CCR9⁺ $\gamma\delta 17$ cells from secondary lymphoid organs into the inflamed pleura via the peripheral blood.

A unifying mechanism of CCL25-dependent T-cell migration is the dependence on the $\alpha 4\beta 7$ integrin. Both in inflammatory pleurisy [5] and in homeostatic gut homing [16], $\alpha 4\beta 7$ neutralization abolished the chemotactic effect of CCL25. Therefore, the coexpression of CCR9 and $\alpha 4\beta 7$ enables ($\gamma\delta$) T cells to migrate to CCL25 gradients, and infiltrate tissues on adhesion and transendothelial crossing mediated by $\alpha 4\beta 7$ interactions with MadCAM-1 and VCAM-1.

Chemokine-mediated $\gamma\delta$ T-cell migration to sites of inflammation

The inflammatory roles of CCL25 are part of a more global program of chemokine-dependent migration by which $\gamma\delta$ T cells respond to breaks in homeostasis, such as challenge with microorganisms or allergens (Fig. 1). Before their current study in this issue of the *European Journal of Immunology* on CCL25 [5], Penido et al. had demonstrated a crucial role for CCL2, a ligand for CCR2, in attracting lymphoid $\gamma\delta$ T cells to the inflamed pleura [4]. They obtained similar results with infectious stimuli, namely *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) or bacterial endotoxin (LPS) [3]. Interestingly, although the β -chemokines CCL3 and CCL5 were also induced in allergic pleurisy (and can mediate $\gamma\delta$ T-cell chemotaxis in vitro), neutralization experiments showed they were not essential for $\gamma\delta$ T-cell recruitment. Thus, only CCL2/CCR2 played a nonredundant role in $\gamma\delta$ T-cell migration to the inflammatory site in vivo [4].

An important difference between these previous studies on CCL2/CCR2 [3, 4] and the current one on CCL25/CCR9 [5] is that, while the former showed an impact on total $\gamma\delta$ T-cell numbers, the latter only affects specifically the $\gamma\delta 17$ subset. Thus, whereas CCR2 seems to be a determinant for $\gamma\delta$ T-cell migration as a whole, CCR9 may be selective for $\gamma\delta 17$ cells. Future studies should explore this possibility in other models of inflammation, and also investigate chemokine-dependent mechanisms that may selectively control the recruitment of IFN- γ^+ $\gamma\delta$ T cells, which are particularly relevant in the context of antitumor immune responses [22].

It is also essential to gain a deeper understanding of the roles played by inflammatory chemokines in physiological responses of human $\gamma\delta$ T cells, which have been shown to migrate in vitro toward CCL2, CCL3, CCL4, CCL5, CXCL10, and CXCL12 [2]. Intriguingly, a study by Brandes et al. has suggested that human $\gamma\delta$ T cells switch, on activation, from an “inflammatory migration profile” (CCR2 $^+$, CCR5 $^+$, CXCR3 $^+$) to a “lymph node homing profile” (CCR7 $^+$), which facilitates their cross-talk with components of the adaptive immune system (B and $\alpha\beta$ T cells) [23].

With regard to the physiological role of human $\gamma\delta$ T cells, these cells are mostly comprised of V $\gamma 9$ V $\delta 2$ cells, which are the dominating subset in the peripheral blood, and V $\delta 1$ cells, which are more abundant in epithelial tissues. Cells from these two subsets isolated from HIV patients have been shown to migrate in vitro preferentially toward CXCL10 (for V $\gamma 9$ V $\delta 2$ cells) and CXCL12 (for V $\delta 1$ cells) [24]; however, it should also be noted that $\gamma\delta$ T cells are themselves important sources of chemokines, especially the

β -chemokines CCL3, CCL4, and CCL5, and therefore can influence immune responses. In fact, both V $\gamma 9$ V $\delta 2$ and V $\delta 1$ can produce high levels of these CCR5 ligands and thus suppress HIV-1 replication in vitro [25, 26].

What is the role of IL-17 and IL-17-producing ($\gamma\delta$) T cells in allergy?

Focusing on allergic reactions, extensive work by Born and colleagues on pulmonary $\gamma\delta$ T cells revealed an interesting dichotomy between a V $\gamma 1^+$ subset that promoted, and a V $\gamma 4^+$ subset that suppressed, airway hyper reactivity (AHR) [27]. None of these effects have, however, been linked to IL-17, even though $\gamma\delta 17$ cells have been independently found in close association with the inflamed airway epithelium [28]. The current paper by Costa et al. [5] thus raises the question of the relevance of $\gamma\delta 17$ cells, and more generally of IL-17, in allergic reactions.

Various studies have found elevated levels of IL-17, and increased numbers of Th17 cells, in the lung and in the peripheral blood of allergic asthmatics [29]. However, results in animal models have been complicated by differences in types of allergens, experimental protocols, and mouse strains [29]. IL-17 seems to be required for granulocytic infiltration in mouse models that employ airway sensitization to allergen (instead of allergen injection) [30]. In fact, allergic airway sensitization produced Th17-cell recruitment to the lung, together with neutrophilia and AHR. This contrasted with the strong Th2 response and eosinophilia, but no AHR, obtained with intra-peritoneal injection of OVA [30]. Furthermore, the adoptive transfer of antigen-specific Th17 cells resulted in neutrophilia and AHR upon subsequent antigen challenge [31]. Interestingly, this Th17-dependent AHR was not sensitive to steroids, contrary to the AHR induced by the adoptive transfer of antigen-specific Th2 cells [31]. Corticosteroids, which inhibit Th2 responses, are the gold standard treatment for asthma, but this treatment fails in some patients that maintain elevated Th2 and Th17 cells and neutrophils, leading to morbidity in severe allergic asthma [29].

Although these studies [29–31] have suggested a pathogenic role for Th17 cells and IL-17 in allergic asthma, a previous report [32] had paradoxically suggested a protective role for this cytokine. The administration of IL-17 in the chronic allergic phase inhibited ongoing Th2 responses, eosinophilia, and bronchial hyper reactivity [32]. This is also consistent with a more recent study by Murdoch and Lloyd [33] showing that $\gamma\delta 17$ cells promote the resolution of airway inflammation and remodeling. Most interestingly, $\gamma\delta$ T cells, which were the main source of IL-17 in the allergic lung, inhibited Th2 responses and reduced AHR when adoptively transferred at the peak of acute inflammation [33]. Importantly, IL-17-deficient $\gamma\delta$ T cells failed to resolve inflammation. These data strongly suggest a regulatory role for $\gamma\delta 17$ cells in allergic reactions.

In the study by Costa et al. [5], it is noteworthy that, even though CCL25 neutralization impaired $\gamma\delta 17$ cell migration, this did not translate into a reduction of the number of total $\gamma\delta$ T cells

in the inflamed pleura [5]. This implies that the vast majority of infiltrated $\gamma\delta$ T cells were actually not producing IL-17. On the other hand, the intra-pleural levels of IL-17 were approximately fivefold lower than those of IL-4, and over tenfold lower than those of IFN- γ . This highlights the importance of understanding the specific contributions of IL-17, $\gamma\delta$ 17, and Th17 cells in allergic reactions mostly dominated by Th2- and Th1-associated cytokines.

Finally, even if the role of $\gamma\delta$ 17 cells in animal models of allergy is becoming clearer, it remains critical to determine whether an equivalent population participates in human allergic reactions. IL-17-producing $\gamma\delta$ T cells are still poorly characterized in human pathology, possibly because they only accumulate—likely in an age-dependent fashion—in extremely inflammatory sites [34]. In allergy, as in infection or tumor immunology, integrating the rapidly evolving knowledge on murine $\gamma\delta$ 17 cells with new and definitive findings in humans will be a major challenge for $\gamma\delta$ T-cell researchers.

Acknowledgments: The author thanks Telma Lança for helpful discussions on this topic, Natacha Gonçalves-Sousa for help preparing the manuscript, and the European Research Council (Starting Grant) and the European Molecular Biology Organization (Young Investigator Programme) for support.

Conflict of interest: The author declares no financial or commercial conflict of interest.

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Abbreviations: AHR: airway hyper reactivity · IEL: intra-epithelial lymphocyte

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See accompanying article:
<http://dx.doi.org/10.1002/eji.201142021>

Received: 19/3/2012

Revised: 21/3/2012

Accepted: 28/3/2012