PLASMA-CELL HOMING

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Recent studies indicate that chemoattractant cytokines (chemokines), together with tissue-specific adhesion molecules, coordinate the migration of antibody-secreting cells (ASCs) from their sites of antigen-driven differentiation in lymphoid tissues to target effector tissues. Developing ASCs downregulate the expression of receptors for lymphoid tissue chemokines and selectively upregulate the expression of chemokine receptors that might target the migration of IgA ASCs to mucosal surfaces, IgG ASCs to sites of tissue inflammation and both types of ASC to the bone marrow — an important site for serum antibody production. By directing plasma-cell homing, chemokines might help to determine the character and efficiency of mucosal, inflammatory and systemic antibody responses.

Humoral immunity is mediated by specific types of antibody secreted by terminally differentiated antibody-secreting B cells (ASCs) known as plasma cells. Tissue-resident plasma cells derive from antigen stimulation of naive or memory B cells in secondary lymphoid tissues such as the spleen or lymph nodes. In response to ligation of their cell-surface immunoglobulin, naive cells undergo clonal expansion and differentiation, developing either into memory cells or ASCs. The first ASCs to arise mainly secrete IgM and initially produce a low-affinity humoral response. Other activated B cells receive co-stimulation by specialized $CD4^+$ T helper cells and form germinal centres, in which class switching, affinity maturation and somatic hypermutation occur. The result is the generation of memory B cells and ASC precursors (plasmablasts) that express high-affinity antibodies for cognate antigen. Plasmablasts can differentiate locally into sessile plasma cells that reside in the secondary lymphoid tissue of origin — a fate that seems particularly common for IgM ASCs — or they can traffic back through the efferent lymph to the blood to populate distant sites. The molecular mechanisms that control plasma-cell development have been reviewed elsewhere in detail[1,2].

Interestingly, the site of antigen presentation and ASC differentiation (together with the nature of the stimulating antigen) determines the main immunoglobulin isotype that is expressed by the induced ASCs, and both the site of induction and the isotype expressed correlate with the homing potential and final tissue distribution of the resulting ASCs. In this review, we examine how recently described tissue-specific chemokines work together with adhesion molecules to mediate the distinct tissue-trafficking patterns of IgA versus IgG ASCs.

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Trafficking patterns of IgG and IgA ASCs

Early studies from the late 1970s found that adoptively transferred lymphocytes from gut-associated lymphoid tissues — for example, the mesenteric lymph nodes or Peyer's patches — populate many mucosal effector sites (that is, the intestine, urogenital tract, mammary glands, salivary glands and respiratory tract) with IgA ASCs[3–6]. Conversely, IgA-secreting plasma-cell precursors that are present in the lymphoid tissues of the upper aerodigestive tract (defined as tissue including the oral cavity, pharyx, larynx, oesophagus, bronchi and lungs) — for example, the mediastinal or tracheo–bronchial lymph nodes — preferentially populate the salivary glands and respiratory tract and show low levels of trafficking to the intestine (FIG. 1a). IgG ASC precursors, whether from peripheral or gut-associated lymph nodes, or the spleen, are largely unable to access mucosal tissues and instead preferentially populate the lymphoid tissues and probably (although not assessed in the classic adoptive-cell-transfer studies) the non-mucosal sites of chronic inflammation (FIG. 1b). These observations indicated that trafficking properties might be a crucial

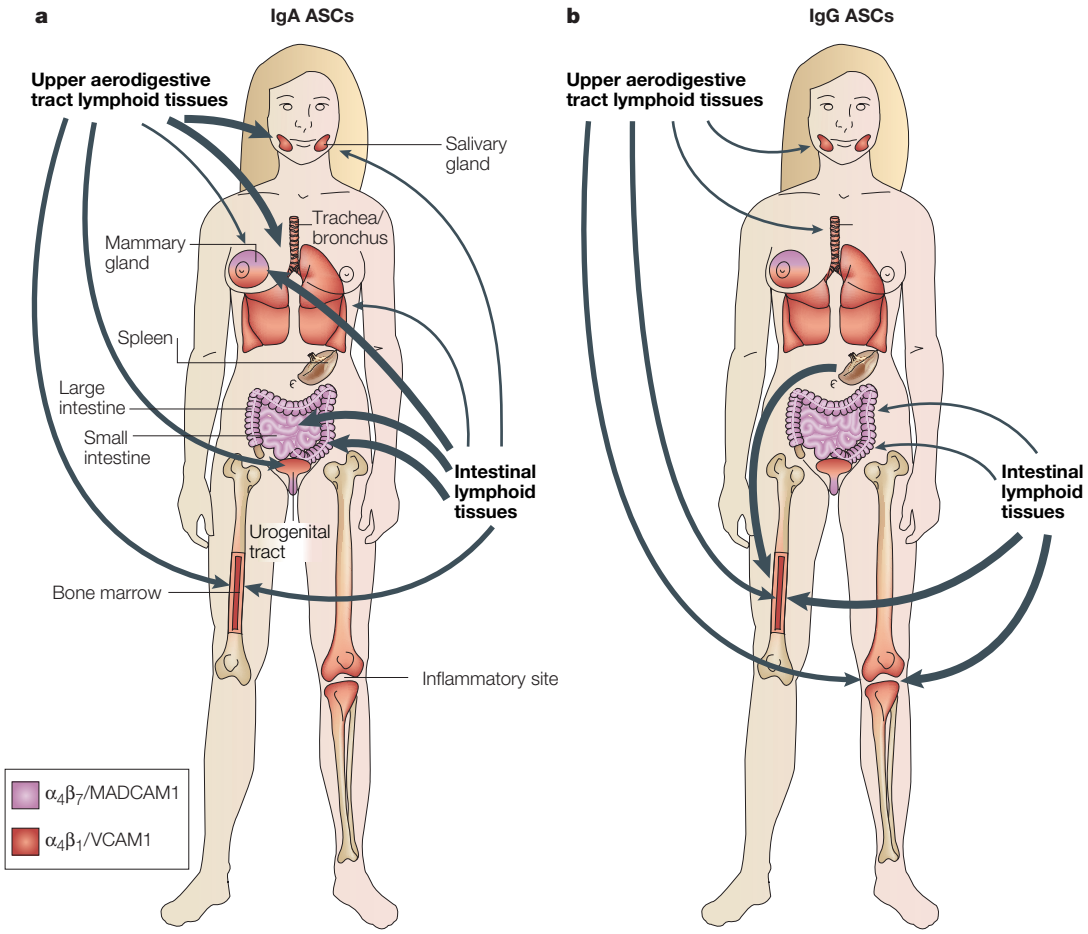


Figure 1 | **IgA and IgG antibody-secreting cells (ASCs) have distinctive trafficking patterns that depend on their site of induction.** IgA ASCs mainly arise in mucosal lymphoid tissues in the gut or the upper aerodigestive tract and have trafficking patterns that are related to their site of induction (**a**). IgG ASCs mainly traffic to the bone marrow or inflammatory sites irrespective of their site of induction (**b**). Part of this specificity is due to the expression of tissue-specific integrin ligands on the endothelium in target tissues. Arrow thickness corresponds to the relative amount of IgA or IgG ASCs that traffic to each site. The colour of the organs corresponds to the expression of the $\alpha_4\beta_7$ integrin ligand mucosal addressin cell-adhesion molecule 1 (MADCAM1) (pink) or the $\alpha_4\beta_1$ (and $\alpha_4\beta_7$) integrin ligand vascular cell-adhesion molecule 1 (VCAM1) (red) that fundamentally subdivides intestinal and non-intestinal tissues (although the mammary gland and urogenital tract seem to express both MADCAM1 and VCAM1).

determinant of the differential tissue localization of IgG versus IgA ASCs. One caveat in interpreting these findings is that the location of ASCs was assessed at least 24 hours after adoptive transfer, giving sufficient time not only for recruitment from the blood, but also for local regulation of ASC numbers by antigen-specific mechanisms of retention and survival. Although the initial recruitment of plasmablasts from the blood into the tissues is antigen independent, local antigen markedly influences the retention of antigen-specific ASCs >8 hours after cell transfer[3]. Nonetheless, these early studies clearly indicated the existence of differential mechanisms for targeting the production of IgA antibody to mucosal surfaces and the production of IgG antibody to lymphoid tissues and sites of inflammation.

Tissue-specific adhesion molecules can account for part of the specificity in IgA versus IgG ASC trafficking (FIG. 1 and BOX 1). A large fraction of IgA ASCs induced in mouse intestinal lymphoid tissues by infection with rotavirus express high levels of the integrin $\alpha_4\beta_7$ (REF. 7) and probably use this receptor to traffic into the intestine, where the $\alpha_4\beta_7$ ligand mucosal addressin cell-adhesion molecule 1 (MADCAM1) is constitutively expressed[8]. Similarly, in humans, most IgA ASCs in the intestinal lamina propria express $\alpha_4\beta_7$ (REF. 9). Moreover, most circulating IgA (and IgG) ASCs induced by oral and rectal immunization bind beads coated with antibody specific for $\alpha_4\beta_7$; whereas ASCs induced at systemic sites are usually unable to bind beads coated with $\alpha_4\beta_7$-specific antibody and instead express L-selectin — a homing receptor that mainly mediates trafficking to lymph nodes by binding carbohydrate ligands. By contrast, most ASCs induced by intranasal immunization co-express L-selectin and $\alpha_4\beta_7$ (REF. 10). Circulating IgG ASCs after systemic immunization were also found to express L-selectin[11]. Most post-capillary venules in non-intestinal mucosal (and non-mucosal) sites lack expression of MADCAM1 and instead express the $\alpha_4\beta_1$ ligand

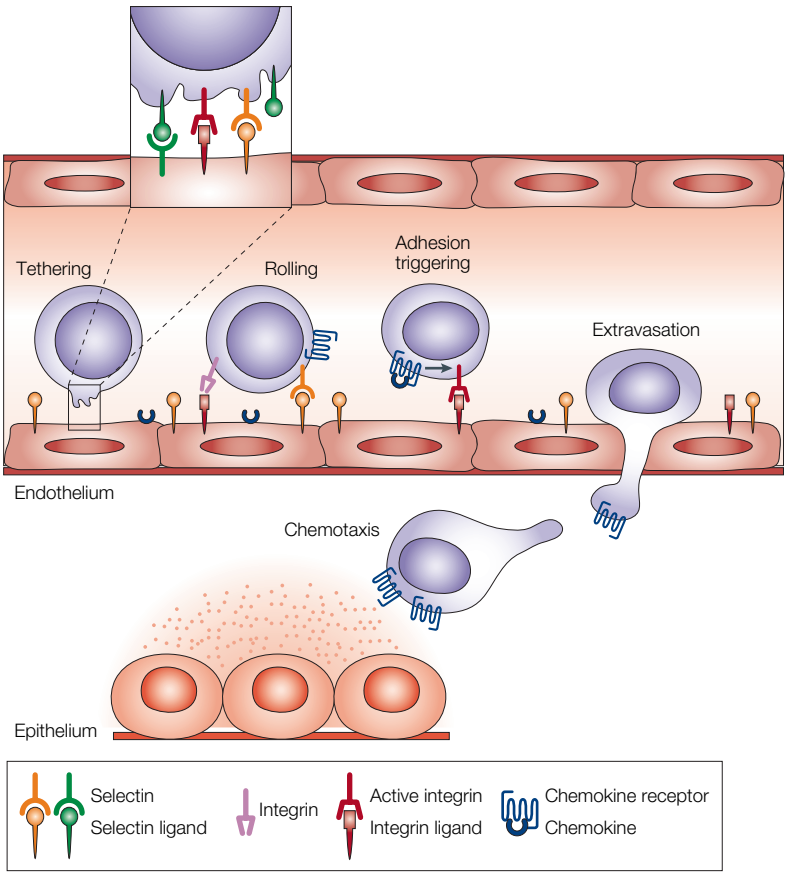
vascular cell-adhesion molecule 1 (VCAM1), although the mammary glands, the urogenital tract and the placenta contain both MADCAM1- and VCAM1-expressing vessels[8]. IgG ASCs induced systemically can express $\alpha_4\beta_1$ (REF. 12), however, it is less clear what level of $\alpha_4\beta_1$ is expressed by $\alpha_4\beta_7$-positive intestinally derived ASCs (although memory B cells that express cell-surface IgA, including the ~60% of cells that are $\alpha_4\beta_7$ positive, also express $\alpha_4\beta_1$ (REF. 13)). The differential interactions of ASCs with VCAM1 versus MADCAM1 are likely to be an important determinant of selective trafficking of IgA versus IgG ASCs, but there is no clear data on the expression of other tissue-specific adhesion molecules such as L-selectin or cutaneous lymphocyte antigen (CLA) that might also contribute to the dissemination of IgG or IgA ASCs. However, the shared vascular expression of VCAM1 by the tissues of the upper aero-digestive tract, in which IgA ASCs predominate, and by the systemic tissues that are selectively populated by IgG ASCs indicates the existence of additional mechanisms of homing selectivity.

The discovery that a factor in mouse colostrum was chemotactic for IgA and IgG ASCs from intestinal (but not peripheral) lymphoid tissues[14] provided the first evidence that chemoattractants might have a role in plasma-cell homing. The studies reviewed here support and extend this hypothesis, pointing to a fundamental role for tissue- and inflammation-specific chemoattractant cytokines, and the regulated expression of their receptors in targeting the production of antibody *in vivo*.

Box 1 | Leukocyte recruitment: a multi-step process

A cascade of adhesive and activation events underlies the trafficking of all subsets of circulating leukocytes that have been examined so far, and will probably hold true for the trafficking of antibody-secreting cells (ASCs). Circulating leukocytes can tether to and roll on the endothelium, generally through transient selectin–carbohydrate ligand interactions and/or integrin $\alpha_4\beta_7$–MADCAM1 (mucosal addressin cell-adhesion molecule 1) or $\alpha_4\beta_1$–VCAM1 (vascular cell-adhesion molecule 1) interactions. Rolling is thought to allow leukocytes to sample the endothelium for signals (such as chemokines, in the case of lymphocytes) that trigger adhesion to the endothelium by activating integrins on the leukocyte surface. Other signals, that might include chemokines, direct the adherent leukocyte to migrate across the endothelium into the extravascular space. Once there, leukocytes can migrate down chemokine gradients towards specific areas such as an epithelial cell surface. Further details about this multi-step process can be found elsewhere[58].

Leukocyte trafficking is a combinatorial process whereby distinct combinations of adhesion molecules and chemokines determine the specificity. This does not mean that components cannot be shared between two leukocyte subsets. For example, the same integrin might be used for triggered adhesion in two distinct tissues, but if the chemokine used to trigger adhesion is different between the two tissues, trafficking specificity is maintained. The adhesion molecules, chemokines and chemokine receptors examined in this review have patterns of expression that correlate well with the trafficking properties of IgA and IgG ASCs, however, the steps in this generalized recruitment process in which each molecule has a role remains to be determined empirically.



Chemokines and plasma-cell homing

CCR7, CXCR5 and CCR6 in B-cell trafficking. During development in the bone marrow, naive B cells gain responsiveness to chemokines that are important for migration into lymph nodes in search of their cognate antigen[15]. These include the ligands of CC-chemokine receptor 7 (CCR7) CC-chemokine ligand 19 (CCL19) and CCL21, the CXC-chemokine receptor 5 (CXCR5) ligand CXCL13, the CCR6 ligand macrophage inflammatory protein 3α (MIP3α, CCL20), and the CXCR4 ligand stromal cell-derived factor 1α (SDF1α, CXCL12). Whereas CCR7-dependent triggering of adhesion is crucial for T-cell recruitment to both intestinal and peripheral lymphoid tissues[16,17], B-cell homing to secondary lymphoid tissues is less dependent on the expression of CCR7 (REFS 16,18). In Peyer's patches — an archetypal intestinal lymphoid tissue — circulating B cells preferentially home through follicle-associated microvessels that often lack expression of the CCR7 ligand CCL21 (REF. 16), but that express the CXCR5 ligand CXCL13 (REF. 18). B-cell recruitment into Peyer's patches involves coordinated, partially redundant signalling through CCR7, CXCR5 and CXCR4 (REF. 18). In peripheral lymphoid tissues, ligation of CXCR4 by CXCL12 synergizes with the interaction between CCR7 and CCL21 in mediating naive B-cell recruitment, but the role of CXCR5 and CXCL13 is markedly reduced compared with their role in Peyer's patches[18].

After they reach a secondary lymphoid tissue, B cells use CXCR5 to localize to follicular zones, in which the stromal cells express CXCL13 (REF. 19). After engagement with antigen, activated B cells increase their responsiveness to CCR7 ligands and migrate towards the T-cell zone, in which the stromal cells express CCL21 and CCL19 (REF. 20), to receive T-cell help. Activated B cells also increase their responsiveness to the CCR6 ligand

Table 1 | **Expression patterns of chemokines involved in trafficking of IgA and IgG ASCs.**

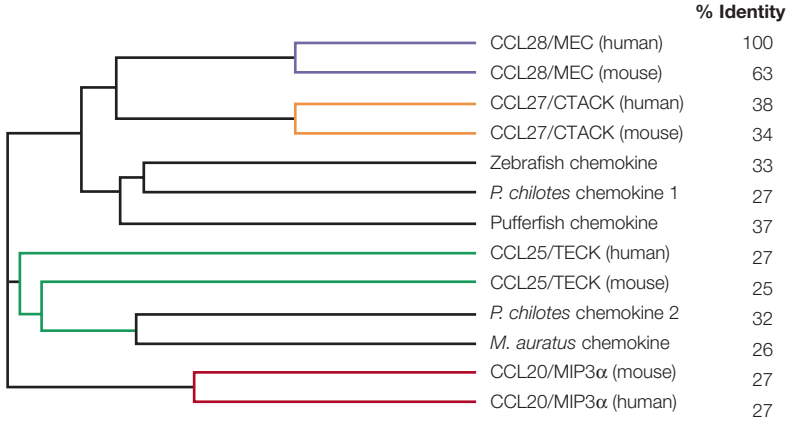
Chemokine	Chemokine-expression pattern	Receptor
CCL25 (TECK)	Small intestinal epithelium and endothelium	CCR9
CCL28 (MEC)	Salivary glands, trachea and brochi, mammary glands, stomach, large intestine, small intestine and bone marrow	CCR10
CCL20 (LARC, MIP3α)	Peyer's patch subepithelial dome and inflamed epithelium	CCR6
CXCL12 (SDF1α)	Bone marrow and gut epithelium	CXCR4
CXCL9 (MIG) and CXCL10 (IP10)	Inflamed tissues	CXCR3

ASC, antibody-secreting cell; CCL, CC-chemokine ligand; CCR, CC-chemokine receptor; CXCL, CXC-chemokine ligand; CXCR, CXC-chemokine receptor; LARC, liver- and activation-regulated chemokine; MEC, mucosa-associated epithelial chemokine; MIG, monokine induced by interferon-γ; MIP3α, macrophage inflammatory protein 3α; SDF1α, stromal cell-derived factor 1α; TECK, thymus-expressed chemokine.

CCL20 (REF. 21) and might use this receptor to localize to the epithelial dome of Peyer's patches — the site of M cell-mediated transport of luminal antigen into the Peyer's patch — as CCL20 is expressed by activated epithelial cells[22] (TABLE 1). B cells that undergo germinal-centre formation downregulate their responsiveness to chemokines (although more so in humans than in mice)[15,23]. Class-switched memory B cells that express IgA or IgG regain responsiveness to CCR7, CXCR5, CCR6 and CXCR4 ligands[23–25], and probably use these receptors to recirculate through secondary lymphoid tissues (FIG. 2). As described later, IgG and IgA memory B cells also gain the expression of additional chemokine receptors that can mediate their entry into non-lymphoid tissues.

Box 2 | **Evolutionary relationship between epithelial chemokines**

Chemokines that are involved in the attraction of IgA antibody-secreting cells (ASCs) are members of a subfamily of conserved, epithelial chemokines that probably evolved to provide protection at exposed epithelial surfaces. When the sequence of human CC-chemokine ligand 28 (CCL28) was compared with proteins in a non-redundant protein database several related chemokines were found. Pairwise comparisons were carried out on truncated sequences from the CC or CXC motifs onward. Marked homology of the mucosal IgA ASC attractant CCL28 (also known as mucosa-associated epithelial chemokine, MEC) is observed with CCL25 (thymus-expressed chemokine, TECK), which is expressed by the small intestine and attracts IgA ASCs and intestinal memory T cells; with CCL20 (macrophage inflammatory protein 3α, MIP3α), which is expressed by activated skin and mucosal epithelia; and with CCL27 (cutaneous T-cell-attracting chemokine, CTACK), which is implicated in T-cell homing to skin. The CCL28 subfamily includes several fish chemokines (including those from zebrafish, pufferfish, *Paralabidochromis chilotes* and *Melanochromis auratus*) that might have evolved from a common epithelial chemokine precursor.



A subset of IgG or IgA class-switched, germinal-centre B cells develop into plasmablasts that leave the lymph nodes or Peyer's patches and migrate through the lymph and blood to tissues where they develop into sessile plasma cells. These early ASCs downregulate responsiveness to chemokines expressed by the lymphoid tissues (FIG. 2). For example, antigen-specific IgG ASCs that arise in the spleen[26–28] reduce their responsiveness to CXCL13, CCL21 and CCL19 while retaining responsiveness to CXCL12, and similarly, few of the circulating IgG ASCs in humans express CXCR5 (REF. 11). Expression of CCR6 (and responsiveness to CCR6) is also lost during ASC differentiation both *in vitro*[24] and *in vivo*[29]. This loss of responsiveness (and/or receptor expression) to lymphoid-tissue chemokines might facilitate the exit of plasmablasts from lymph nodes. As discussed later, their subsequent trafficking to extra-lymphoid sites is achieved by the parallel upregulation of expression of receptors for tissue- or inflammation-selective chemokines.

CXCR4 and trafficking to the bone marrow. The bone marrow is an important site for the production of serum antibody and it contains a large number of IgG and IgM ASCs, and a smaller number of IgA ASCs. Both systemically induced IgG ASCs and intestinally induced IgA ASCs can populate the bone marrow[7,27,28] during an immune response (FIG. 1). CXCL12 is highly expressed by stromal cells in the bone marrow where it has a crucial role in the development and retention of B-cell progenitors[30,31]. The ability of IgG ASCs to migrate to the bone marrow correlates with their expression of CXCR4 and their responsiveness to CXCL12. In chimeric mice that were reconstituted with CXCR4-deficient fetal-liver cells and then immunized, the induced IgG ASCs were mislocated to the marginal zone of the spleen, circulating IgG ASCs were increased and fewer IgG ASCs accumulated in the bone marrow[27], supporting a role for CXCR4 in bone-marrow localization. Because IgA ASCs in mucosal lymphoid tissues maintain responsiveness to CXCL12 (REFS 29,32), CXCR4 can probably mediate trafficking of IgA-secreting plasma cells to the bone marrow as well (FIG. 3). CXCL12 can also be expressed by the epithelium in mucosal tissues[33], and might additionally contribute to the localization, survival or other functions of IgA ASCs in mucosal sites. Other chemokines and receptors might

also have a role in the localization of ASCs to the bone marrow. Most ASCs in the bone marrow and many circulating CD38$^+$ ASCs (of undetermined isotype) express CXCR6 for example, the ligand of which, CXCL16, is expressed by the bone-marrow compartment[34]. Interestingly, messenger RNA encoding CCL28 has also been detected by polymerase chain reaction (PCR) in the bone marrow[34] and might participate in the recruitment of CCR10-expressing cells (particularly IgA ASCs, see later) to this site as well.

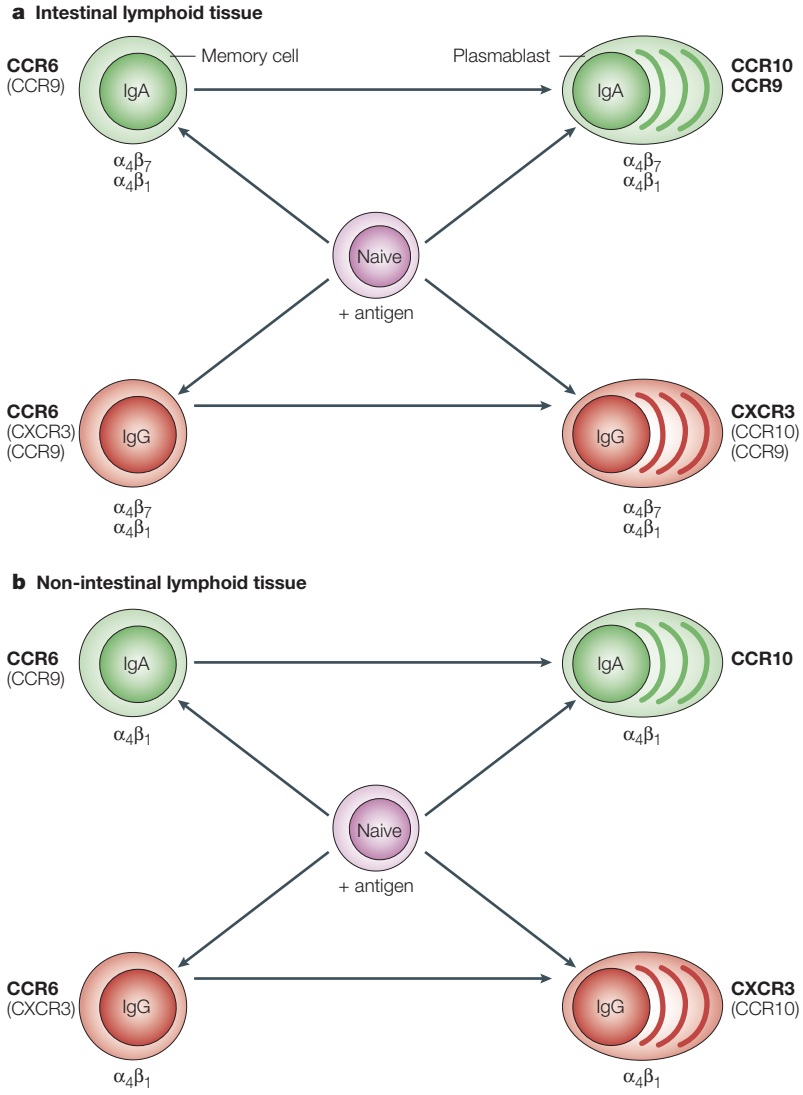


Figure 2 | **Changes in the expression of chemokine receptors during B-cell differentiation.** The differentiation of B cells in intestinal (**a**) versus non-intestinal (**b**) lymphoid tissues alters the trafficking phenotype of both memory cells and plasmablasts. Naive B cells (CCR7$^+$CXCR5$^+$CCR6$^+$CXCR4$^+$) in lymphoid tissues can differentiate directly into plasmablasts or become memory B cells that subsequently encounter the same antigen and then become plasmablasts. Differentiation of B cells in the lymphoid tissues of the small intestine is associated with the upregulation of expression of $\alpha_4\beta_7$ integrin and CC-chemokine receptor 9 (CCR9). The differentiation of IgA plasmablasts is associated with the expression of CCR10, irrespective of the site of induction (resulting in a subset of CCR9$^+$CCR10$^+$ IgA ASCs). The differentiation of IgG plasmablasts is correlated with the upregulation of expression of CXC-chemokine receptor 3 (CXCR3), irrespective of site of induction. All memory cells retain expression of CXCR5, CCR7 and CXCR4, and plasmablasts retain expression of CXCR4. Chemokine receptors with less importance in non-lymphoid tissue trafficking for a given subset of ASCs are shown in parenthesis.

CXCR3 and trafficking to inflammatory sites. IgG ASCs are commonly found in chronic inflammatory sites, such as the synovium of patients with rheumatoid arthritis[35]. Although some of these IgG ASCs might arise locally in the lymphoid follicles that are induced in non-lymphoid sites during severe inflammation[36,37], others probably migrate to inflammatory sites. Antigen-specific IgG ASCs induced in the spleen temporarily upregulate their expression of CXCR3 (FIG. 2) and responsiveness to the CXCR3 ligands monokine-induced by interferon-γ (MIG, CXCL9) and IP10 (CXCL10)[28]. Interestingly, putative IgG ASCs in the bone marrow seem to lack expression of CXCR3 (REF. 34) and might have downregulated the expression of this chemokine receptor after homing to the bone marrow, or they might be a subset of IgG ASCs that never upregulate the expression of this receptor. CXCR3 ligands are widely expressed by the endothelium and other cells in inflamed tissues[38], indicating that circulating IgG-secreting plasmablasts that express CXCR3 can directly enter these sites from the blood (FIG. 3). It remains to be seen whether the expression of CXCR3 is directly linked to IgG class switching or whether CXCR3 expression was coordinately regulated under the experimental conditions examined.

CCR9 and CCR10 in trafficking to mucosal tissues. IgA ASCs in mucosal lymphoid tissues can upregulate the expression of two chemokine receptors, CCR9 and CCR10, which are associated with the mucosal tissue trafficking patterns of these cells (FIG. 2). Responsiveness to the CCR9 ligand CCL25 is a characteristic of mouse IgA ASCs in Peyer's patches and mesenteric lymph nodes, but not those in lymphoid tissues of the upper aerodigestive tract[32,39], indicating that the expression of CCR9 is induced during the development of IgA ASCs in the lymphoid tissues of the intestinal mucosa. Similarly, in humans, CCR9-expressing IgA ASCs are abundant in the appendix, but are rarer in the tonsil[29]. Moreover, CCR9 expression seems to be associated specifically with cells that are induced by antigens presented in the small intestine. Infection with the small intestinal pathogen rotavirus, for example, leads to the induction of virus-specific IgA ASCs that migrate in response to CCL25 (REF. 39). Most IgA ASCs in the lamina propria of the small intestine are CCR9 positive, whereas expression of CCR9 by IgA ASCs from other segments of the gut is rare[29], and CCR9 is not expressed by IgA ASCs in the lungs[29,32]. Consistent with this restricted receptor expression, the CCR9 ligand CCL25 is expressed at high levels by crypt epithelial cells[40] and endothelial cells[41] in the small intestine, but shows low levels of or no expression at other mucosal sites. So, CCR9 and CCL25, which also mediate the homing of a specialized subset of memory T cells to the small intestine[40–42], seem ideally suited to focus the immune response to antigens in the small intestine.

By contrast, the CCR10 ligand CCL28 is produced by epithelial cells in various mucosal tissues (for example, the large intestine, stomach, trachea and bronchi, mammary glands and salivary glands)[43–45] indicating a broad role for this chemokine in mucosal immunity (FIG. 3).

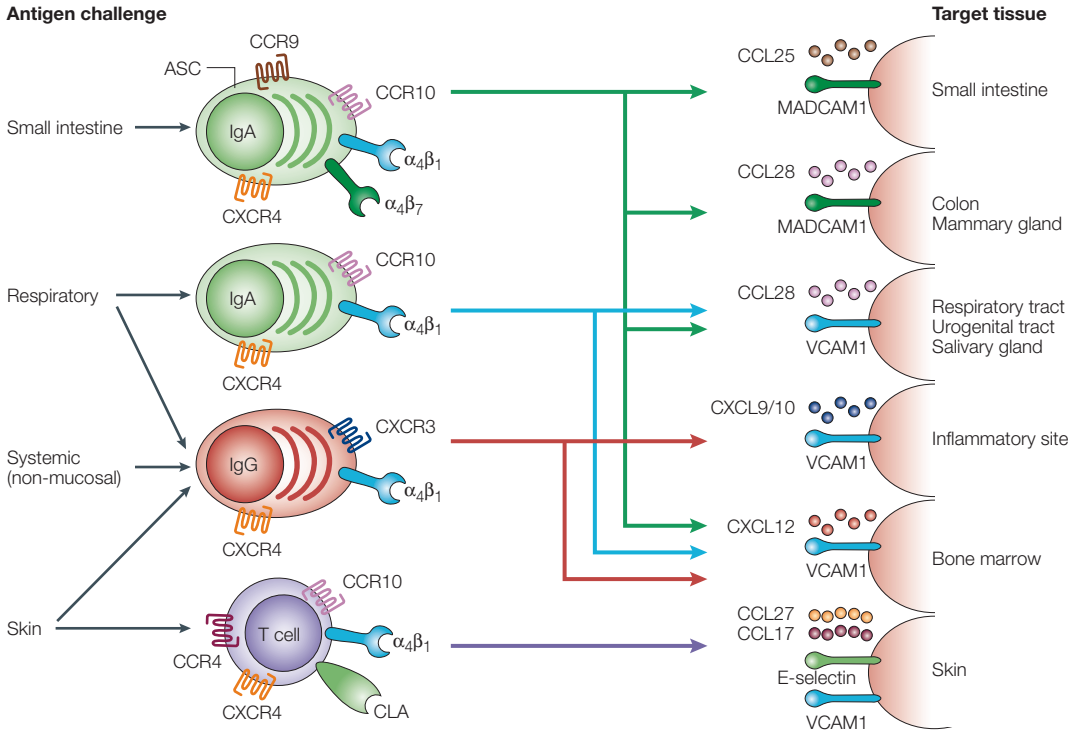


Figure 3 | **Model of trafficking of IgA and IgG ASCs mediated by specific adhesion molecules and chemokine receptors.** Successful recruitment of lymphoid cells into a target tissue requires both specific chemokine recognition and appropriate adhesion/homing-receptor engagement. In this model, IgA antibody-secreting cells (ASCs) induced in the small intestine can enter all mucosal sites, whereas those that are induced by respiratory antigen lack the expression of CC-chemokine receptor 9 (CCR9) and $\alpha_4\beta_7$, and so are restricted in their trafficking to non-intestinal mucosal tissues and the bone marrow. IgG ASCs express CXC-chemokine receptor 3 (CXCR3) and $\alpha_4\beta_1$, and are targeted to inflamed non-mucosal tissues and the bone marrow. Skin-homing T cells are illustrated for comparison: these cells express CCR10, but cannot traffic to mucosal sites because they lack expression of $\alpha_4\beta_7$. Conversely, IgA ASCs lack expression of the skin-homing receptor cutaneous lymphocyte antigen (CLA) — a ligand for vascular E-selectin. The induction of expression of particular chemokine receptors by IgA versus IgG ASCs together with the expression of tissue-specific chemokines correlates well with the trafficking of ASCs throughout the body. The colour of the receptors expressed by the lymphocytes correlates with the colour of their ligands expressed by the tissues. MADCAM1, mucosal addressin cell-adhesion molecule 1; VCAM1, vascular cell-adhesion molecule 1.

In fact, almost all IgA ASCs (whether they are from intestinal or non-intestinal lymphoid tissues or mucosal effector tissues) express CCR10 and respond to CCL28 (REFS 29,32,45) (FIG. 2). Surprisingly, even IgA ASCs in the small intestine express CCR10 (REF. 29). In mice, approximately half of the IgA ASCs in the gut wall can be derived from B1 lineage B-cell precursors[46], although the pathway of migration and sites of maturation of these ASCs are uncertain and controversial[47,48]. The essentially universal expression of CCR10 by IgA ASCs of the lamina propria argues that B1-derived IgA-secreting plasma cells, as well as the conventional B2-derived IgA-secreting plasma cells, express this shared mucosal trafficking receptor. By contrast, few IgG or IgM ASCs are CCR10 positive, re-emphasizing the selective association of this receptor with IgA ASCs.

The expression of the CCR10 ligand CCL28 by various mucosal epithelial tissues is probably the missing link that allows intestinal IgA ASCs to populate various mucosal sites — a hallmark of the common mucosal IgA immune system[4]. The unique patterns of expression of CCR9 and CCR10 might also help to explain the differences in dissemination of antigen-specific IgA after nasal or oral immunization, which is likely, although not proven in humans, to be a result of differential migration properties. In both humans and mice, oral immunization leads to the presence of antigen-specific IgA in both intestinal and non-intestinal mucosal tissues, such as the salivary glands, the respiratory tract and the mammary glands[6,49,50]. Conversely, nasal immunization leads to a more restricted distribution of antigen-specific IgA in the upper aerodigestive tract and the urogenital tract[51–53]. The upregulation of expression of CCR10, but not CCR9, and the expression of $\alpha_4\beta_1$, but not $\alpha_4\beta_7$, by IgA ASCs induced in the lymphoid tissues of the upper aerodigestive tract after intranasal immunization would allow their trafficking to tissue sites that express VCAM1 and the CCR10 ligand CCL28. So, nasally induced IgA ASCs would traffic efficiently to the salivary glands, respiratory tract and urogenital tract, but not to the intestine (especially the small intestine) (FIG. 3). By contrast, the induction of expression of CCR9 as well as CCR10, and the expression of $\alpha_4\beta_7$ in addition to $\alpha_4\beta_1$ by intestinally derived IgA ASCs after oral immunization should allow trafficking to sites that express CCL28 or CCL25 together with

either MADCAM1 or VCAM1 — that is, to essentially all mucosal tissues, including the small intestine (FIG. 3). It is possible that selective antigen challenge in the colon could induce IgA-secreting plasmablasts that express CCR10 and $\alpha_4\beta_7$ without expression of CCR9, and these cells would be expected to traffic preferentially back to the colon. Appropriate induction of expression of these receptors for IgA-secreting plasma-cell trafficking might be an important criterion for the success of vaccination protocols that are designed to provide protection at mucosal surfaces.

It is intriguing that the two chemokines that attract IgA ASCs CCL28 and CCL25 have marked homology and belong to a subfamily of chemokines that are selectively expressed by epithelial cells (BOX 2). Other members of this subfamily include the keratinocyte-expressed chemokine CCL27, also known as cutaneous T-cell-attracting chemokine (CTACK)[54], which is a second ligand for CCR10, and CCL20, the CCR6 ligand. These chemokines seem to have evolved to coordinate immunity at exposed epithelial surfaces. CCL20 is expressed not only by lymphoid tissue-associated intestinal epithelium (such as the dome of Peyer's patches or inflamed gut epithelium)[22,55], but also by inflamed epithelial cells in the lungs or skin[56]. As mentioned earlier, CCR6 is expressed by naive B cells but becomes functionally active only after cross linking of cell-surface expressed immunoglobulin. So, the regulated expression of CCL20 might help to recruit circulating memory B cells to sites of inflammation. CCL27 is of interest because even though, similar to CCL28, it is a ligand for CCR10, its role seems to be limited to the recruitment of cutaneous memory T cells[54,57]. IgA ASCs respond to CCL27 *in vitro*, but probably lack expression of CLA — a homing receptor for E-selectin, which is required for efficient recruitment of CCR10-expressing T cells to the skin (FIG. 3).

Interestingly, CCR10 is not expressed by memory B cells in the circulation or in mucosal tissues[29]. By contrast, CCR9 is expressed by a subset of memory B cells that express either IgG or IgA[29] and might facilitate their entry directly into the small intestine. It remains to be seen whether the transcriptional complexes that control class-switch recombination to secreted IgA[2] also control CCR9 and/or CCR10 expression, or whether distinct molecular mechanisms that regulate chemokine-receptor expression and IgA production are merely coordinately engaged during the development of ASCs in the mucosal immune environment.

Up to 15% of circulating IgG ASCs express low levels of CCR10 (REF. 29), which might help to mediate their localization to mucosal epithelial tissues (in particular, to tissues of the upper respiratory tract). However, if these same IgG ASCs also lack high levels of $\alpha_4\beta_7$ expression, their relatively low level of expression of CCR10 could also help to explain the low frequency of IgG ASCs that are normally present in intestinal mucosal tissues. At the same time, low levels of CCR10 expression, together with CXCR3 expression (and CLA expression), could facilitate the recruitment of IgG ASCs to the skin (where the other CCR10 ligand CCL27 is expressed[54]) during chronic inflammation.

Conclusions

Increasing evidence indicates that chemokines have a central role in the regional targeting of humoral and secretory antibody production. Together with the differential expression of α_4 integrin receptors for MADCAM1 or VCAM1, the patterns of chemokine-receptor expression by ASCs provide a reasonable explanation for the predominant localization of IgG ASCs to inflammatory sites; for the widespread mucosal dissemination of IgA ASCs that respond to intestinal antigens; for the more restricted localization of respiratory IgA responses and for the abundance of both IgG and IgA ASCs in the bone marrow. Nevertheless, the role of chemokines in the recruitment process remains to be formally shown through chemokine-blocking or gene-knockout studies. It will also be important to assess any differences in the role of chemokines in plasma-cell trafficking between humans and mice; to determine the role of chemokines in plasma-cell retention and survival; to identify the regulatory mechanisms that underlie the co-expression of IgA with mucosal chemokine receptors and of IgG with inflammatory chemokine receptors during the differentiation of ASCs; and finally, to elucidate the trafficking properties of IgE ASCs. A detailed understanding of the molecular mechanisms that target local antibody production could have implications for the development of vaccines against mucosal pathogens, and could lead to new approaches for manipulating humoral immunity in autoimmune and allergic diseases.

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