Zhang and Yao
Inflammation and Regeneration (2024) 44:21
https://doi.org/10.1186/s41232-024-00334-5

Inflammation and Regeneration

REVIEW

Open Access

Immune cell trafficking: a novel perspective on the gut-skin axis

Jiayan Zhang[1,2,3] and Zhirong Yao[1,2,3*]

Abstract

Immune cell trafficking, an essential mechanism for maintaining immunological homeostasis and mounting effective responses to infections, operates under a stringent regulatory framework. Recent advances have shed light on the perturbation of cell migration patterns, highlighting how such disturbances can propagate inflammatory diseases from their origin to distal organs. This review collates and discusses current evidence that demonstrates atypical communication between the gut and skin, which are conventionally viewed as distinct immunological spheres, in the milieu of inflammation. We focus on the aberrant, reciprocal translocation of immune cells along the gut-skin axis as a pivotal factor linking intestinal and dermatological inflammatory conditions. Recognizing that the translation of these findings into clinical practices is nascent, we suggest that therapeutic strategies aimed at modulating the axis may offer substantial benefits in mitigating the widespread impact of inflammatory diseases.

Keywords Gut-skin axis, Immune cell trafficking, Inflammatory diseases

Background

The skin and gut constitute the two largest immune systems in the human body and employ distinct defense strategies. However, inflammatory diseases frequently co-occur in these sites. Patients with inflammatory bowel disease (IBD) are known to have an increased risk of inflammatory skin disorders [1–3]; conversely, individuals with primary dermatologic conditions exhibit increased susceptibility to IBD [4–6]. While a shared genetic predisposition may signal an increased risk for concurrent skin and gastrointestinal diseases [7], biological communication between the gut and skin is another plausible explanation.

Recent studies have highlighted this bidirectional influence [8, 9]. Specifically, metabolites derived from the gut microbiome such as short-chain fatty acids [10], bile acids [11], and vitamins, as well as neurotransmitters and hormones originating from the gut [12–16], circulate through the blood and affect skin barrier function. Conversely, the skin can produce soluble factors that impact gut health. For instance, compromised skin may release inflammatory cytokines or metabolites that induce or exacerbate gastrointestinal inflammation [17–19].

Beyond the transport of biomolecules through the bloodstream, mounting evidence suggests that the migration of immune cells between the skin and gut during states of immunological imbalance might be a conduit for the spread of pathological conditions and the resultant tissue damage [20, 21]. In fact, the critical role of cell trafficking in the pathogenesis of various diseases has gained increasing recognition in recent years. For example, the development of pathogenic Th17 cells in the small intestine, driven by long-chain fatty acids, has been implicated in disease progression in animal models of central nervous system-mediated inflammation [20]. It has been proposed that complications of IBD such as primary

*Correspondence:
Zhirong Yao
yaozhirong@xinhuamed.com.cn
[1] Dermatology Center, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
[2] Department of Dermatology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
[3] Institute of Dermatology, Shanghai Jiaotong University School of Medicine, Shanghai, China

sclerosing cholangitis (PSC) may be mediated by gut-educated lymphocytes, which are recruited in response to the aberrant expression of gut-homing molecules, including MAdCAM-1 and CCL25, within the liver [22, 23]. Similarly, an active homing axis between the gut and inflamed joints has been reported in patients with ankylosing spondylitis, characterized by cells expressing the $\alpha_4\beta_7$ integrin in inflamed joints and the upregulation of MadCAM-1 in the endothelium [24]. However, while the ectopic expression of gut-associated addressins in skin is an attractive hypothesis for cutaneous extraintestinal manifestations (cEIM), direct evidence in the skin is lacking [25]. The questions of whether abnormal migration of immune cells between the gut and skin can account for the comorbidity of gut and skin inflammation, and what mechanisms underlie such aberrant cell trafficking along the gut-skin axis, remain to be elucidated.

This review delineates the molecular mechanisms of cell migration, the immune architectures of the gut and skin, and the established mechanisms of tissue-specific leukocyte imprinting. It further compiles evidence of immune cell trafficking between the gut and skin in disease states, dissects the underlying mechanisms, and assesses the implications for therapeutic intervention.

Immune cell trafficking

Cell trafficking plays pivotal roles in both the host defense against pathogens and the establishment of immune tolerance. By migrating to specialized microenvironments, immune cells experience functional modulation to shape local immunity and influence inflammatory responses [26]. The intricate process of trafficking encompasses various types of movements, such as homing, retention, recirculation, and amoeboid movement [27, 28]. Although these processes are defined separately, the transitions between them are flexible in a living organism.

Homing

Immune cells are equipped with programmed homing receptors designed to identify tissue-specific adhesion molecules and chemoattractants, thus ensuring the timely allocation of immune effector mechanisms [29]. Homing follows a multistep adhesion cascade (Fig. 1). Initially, selectins and integrins on the surface of immune cells engage with their respective ligands on the vascular endothelium, mediating "tethering" and "rolling" of leukocytes along the vessel wall. Subsequently, endothelial-presented chemokines activate G protein-coupled receptors on leukocytes [30, 31], triggering integrin β subunit cytoplasmic tails to bind with talin [32]. Such binding induces conformational changes of the integrin extracellular domains into high-affinity, extended forms [33–35], leading to the firm "arrest" of cells on the luminal face of postcapillary venules. The leukocytes then navigate through the endothelial junctions, propelled by shear forces, adhesive interactions, and chemoattractant gradients, finally disseminating into designated microenvironmental niches [36].

Retention

Immune cells can be resident in tissues, and this localization is integral to their role in innate and adaptive responses. Innate immune cells are seeded directly into tissues following their development during early embryonic and fetal stages. This process is orchestrated by distinct waves of hematopoiesis that give rise to specialized precursor cells, which subsequently seed developing tissues and acquire tissue-specific phenotypes [43, 44]. In contrast, lymphocytes, the cellular components of adaptive immunity, can take up residence in peripheral tissues following antigen encounter. Upon tissue entry, these cells, including tissue-resident memory T and B cells, coordinate antipathogen immunity and provide long-term protection against future infectious challenges [45].

The retention of immune cells in tissues is mediated by the upregulation of specific markers. Key markers of tissue-resident lymphocytes include CD69, CD103 ($\alpha_E\beta_7$), CD49a, and CD49b. CD69, serving as an endogenous negative regulator, interacts with sphingosine 1-phosphate receptor 1 (S1PR1) in cis to mediate internalization and degradation of this receptor [46]. Given that the chemotactic ligand for S1PR1, sphingosine 1-phosphate (S1P), is abundant in blood and lymph but scant in tissues, CD69 impedes the egress of cells following the S1P gradient [47, 48]. CD103 binds E-cadherin on epithelial cells, thereby promoting cell accumulation in intestinal, cutaneous, bronchial, and genital epithelia [49, 50]. CD49a and CD49b are collagen-binding integrins that primarily adhere to type IV and I collagen [51–53]. Other molecules, such as antigen-specific T cell receptors [54, 55] and some chemokine receptors [56–58] (e.g., CXCR4 and CCR7), are also implicated in cell retention through recognition of cognate antigens or constitutively expressed chemotactic ligands by structural cells [57]. Collectively, immune cells enhance their retention capacity upon inflammatory cytokine response [59] or T cell receptor stimulation, thereby performing tissue-specific functions in immunity [45, 60].

Recirculation and amoeboid migration

Immune cell recirculation connects various microenvironments and involves a range of cells, including dendritic cells (DCs), lymphocytes, monocytes, and granulocytes. These cells migrate through the afferent lymphatics from non-lymphoid tissues into draining lymph nodes and may then travel to adjacent lymph nodes. The

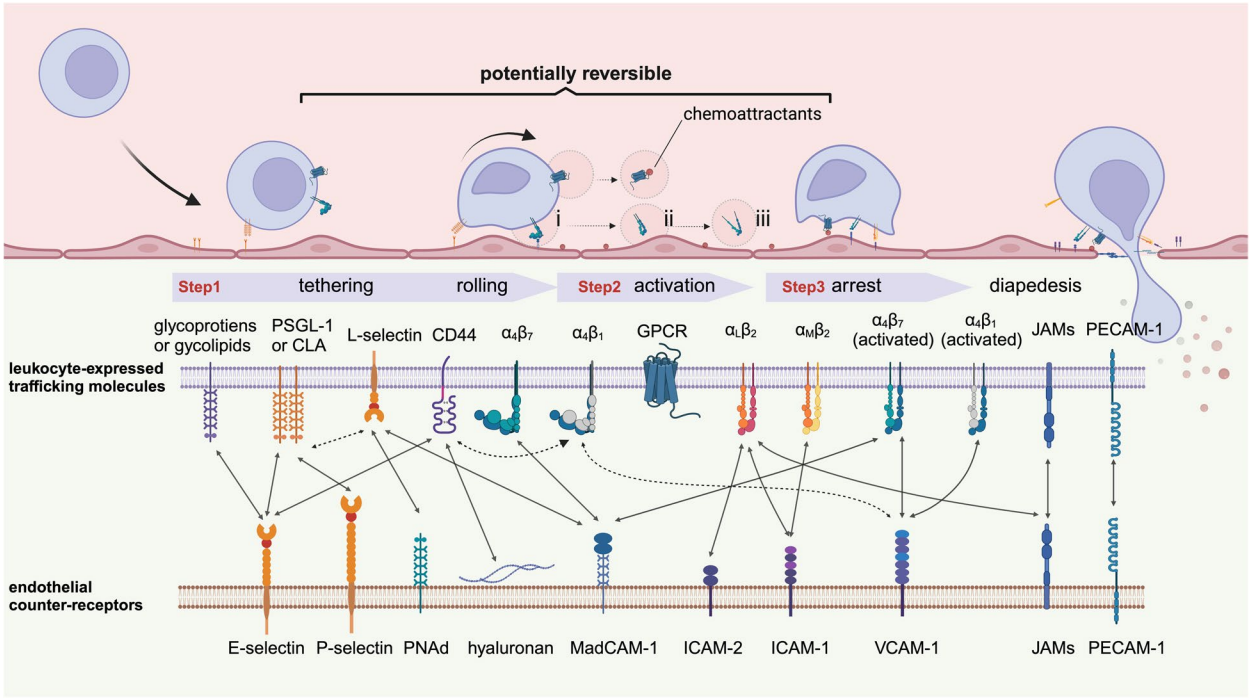

Fig. 1 Multistep homing process of lymphocytes. The top panel depicts the multistep adhesion cascade involved in lymphocyte homing: step 1: tethering and rolling. Tethering is mediated primarily by selectins, which can engage with their ligands rapidly with high tensile strength, enabling the capture of leukocytes out of the bloodstream. Integrins facilitate leukocytes' slower rolling along endothelial cells following capture [37–39]. The adhesive interactions in this step are notably reversible and transient. Step 2: integrin activation. External stimuli are required for integrin affinity modulation [40]. Integrins have three conformational states with differing affinities [40]: (i) bent head-piece conformation with low affinity, (ii) extended head-piece conformation with intermediate affinity, and (iii) extended head-piece conformation with high affinity. Specific endothelial chemokines can rapidly (within milliseconds) enhance integrin affinity [41]. Step 3: arrest. This step is mediated by activated integrins, whereby lymphocytes adhere firmly to the endothelium and come to a complete stop. The bottom of the diagram shows the predominant molecules expressed on lymphocytes and endothelial cells involved at each step [27, 29, 42].. The arrows between them represent potential interactions (broken arrows indicate weak binding)

detailed mechanisms of their entry and migration within afferent lymphatics have been thoroughly reviewed elsewhere [61]. Furthermore, some of these cells can re-enter the bloodstream through an S1P-driven mechanism [62, 63].

The locomotion of immune cells within tissues is orchestrated by amoeboid migration, a multiscale phenomenon coupling cell shape changes, biochemical signaling, and cytosolic and extracellular fluid flows [64, 65].

The immunological anatomy of the skin and intestinal mucosa

Skin immune system

The skin consists of the epidermis and dermis, demarcated by the basement membrane zone. The epidermis is predominantly composed of keratinocytes, supplemented by a minor fraction of T cells and Langerhans cells (LCs) [66]. Depending on the degree of keratinocyte differentiation, the epidermis can be stratified from the outermost to the innermost layer into the stratum corneum, granulosum, stratum spinosum, and stratum basale (Fig. 2a). The stratum corneum is the epidermis's most unique anatomical feature and serves as a barrier that impedes the permeation of water and water-soluble substances, as well as prevents the entry of external pathogens. Beyond their role as a physical barrier, keratinocytes are also instrumental in recruiting immune cells to the epithelial interface, where they regulate cell survival and retention [67]. LCs are professional antigen-presenting cells (APCs) embedded among keratinocytes [68]. Upon activation, they downregulate E-cadherin and upregulate CCR7 to migrate to skin-draining lymph nodes and prime naive T cells, initiating immune responses that may either induce immunological tolerance or spur the expansion of pro-inflammatory effector and memory T cell populations [69].

The dermis, consisting of fibroblasts and connective tissue, provides essential structural support to the skin [76]. Cells traverse to and from the skin via vascular and lymphatic vessels in the dermis, resulting in a higher

cellular diversity in the dermal compartment compared to the epidermis (Fig. 2a) [77–79]. Following skin immunization, dermal dendritic cells (dDCs) migrate to lymph nodes faster than LCs [69], and certain subsets of dDCs tend to move into the outer paracortex to regulate the differentiation of B cells [80, 81]. In healthy skin, dermal macrophages remain unable to migrate to draining lymph nodes.

Skin appendages, which extend from the epidermis into the dermis, provide critical niches for microbial colonization and transdermal penetration of various compounds due to their invaginated architecture and absence of a stratum corneum [82]. They also represent unique immunological sites. Hair follicles offer protection to LCs from environmental damage, such as ultraviolet radiation, thus preserving a reservoir of APCs [83]. Sebaceous and sweat glands contribute to the immune response by secreting chemokines, cytokines, and antimicrobial peptides [84, 85].

Intestinal immune system

In contrast to the skin, the gastrointestinal tract lacks a stratum corneum and is therefore more permeable. As a result, it is continuously exposed to antigens and immune modulators derived from diet and the microbiome. Functionally, the intestinal immune compartment can be divided into inductive sites and effector sites, the former being gut-associated lymphoid tissue (GALT) and the latter encompassing the epithelium and lamina propria [86]. Among the intestinal epithelial cells reside intraepithelial lymphocytes (IELs). The immune cells present in the lamina propria include DCs, macrophages, mast cells, granulocytes, NK cells, γδ T cells, innate lymphoid cells (ILCs), αβ T cells, and B cells [87, 88]. Macrophages in the gastrointestinal tract exhibit a remarkable functional diversity, adapted to the specific ecological niches they inhabit. They are distributed among neurons, blood vessels, Peyer's patches (PPs), crypts, and the epithelium. Notably, macrophages residing in the lamina propria possess high phagocytic capacity and can present antigens to DCs to induce oral tolerance [89]. In humans, GALT consists primarily of PPs, isolated lymphoid follicles (ILFs), MLNs, and lymphoid tissues in the appendix and rectum. T or B cells activated within PPs can migrate to MLNs for further proliferation and differentiation [90, 91].

Strictly speaking, the mucosa does not include MLNs as it consists of the epithelium, lamina propria, and muscularis mucosae (Fig. 2b). However, MLNs play a pivotal role in mucosal immune responses (as detailed later). Lamina propria DCs (lpDCs) sample lumen antigens without disrupting tight junctions and migrate to the MLNs by upregulating CCR7, where they prime naive T cells to differentiate into regulatory or effector subsets [92]. Interestingly, not only lpDCs but also some DCs from PPs and ILFs migrate to MLNs in a CCR7-dependent manner. Yet, under steady-state conditions, DCs do not exit from MLNs into efferent lymphatics [93, 94]. In all, the trafficking of immune cells from mucosal inductive to effector tissues via the lymphatic system forms the cellular foundation for the immune response in the gastrointestinal tract [95].

Immune cell trafficking along the gut-skin axes

Tissue-specific imprinting of leukocytes homing

Prevailing dogma holds that priming of immune cells in specific inductive regions leads to distinct homing

(See figure on next page.)

Fig. 2 **a** The structure and immune cell distribution of the skin under steady state. The epidermis represents the outermost layer of the skin. The dermis can be divided into the superficial papillary layer and the deeper reticular layer. Blood and lymphatic vessels, as well as nerves (not shown), pervade the dermis. Under normal conditions, the most common immune cells in human epidermis are LCs, located in the stratum spinosum, and $CD8^+$ tissue-resident memory T (TRM) cells, found in the stratum basale and stratum spinosum [70]. $CD8^+$ TRM cells can migrate between the epidermis and the papillary dermis, performing tissue patrols [71]. The mouse epidermis contains dendritic epidermal T cells (DETCs), a cell type absent in humans. In healthy skin, dermal leukocytes encompass DCs, macrophages, mast cells, γδ T cells, natural killer (NK) cells, innate lymphoid cells (ILCs), αβ T cells, and B cells. Most αβ T cells in the dermis are $CD4^+$ T cells, while B cells are rarely present in normal skin [72]. Skin appendages include hair follicles, sebaceous glands, and sweat glands (not shown). Commensal microorganisms inhabit the epidermis, dermis, and dermal appendages, forming an additional layer of host defense [73]. **b** Epithelial composition and immune cell distribution of the intestine under steady state. The intestinal epithelium is composed of a single layer of cells, arrayed into projections known as villi which extend into the intestinal lumen, and moat-like invaginations called crypts that surround the villi. Multipotent stem cells are located at the base of these crypts, interspersed among Paneth cells. These stem cells have the capability to differentiate into intestinal absorptive cells and all types of specialized epithelial cells, including goblet cells, Paneth cells, microfold-cells (M-cells), and tuft cells [74]. Intraepithelial lymphocytes (IELs) display high levels of activity. They are typically situated between the basement membrane and the epithelial layer of the intestinal villi under steady-state conditions, occasionally demonstrating transient movements closely associated with epithelial cells [75]. Peyer's patches (PPs) are unique tertiary lymphoid organs in the small intestine, and isolated lymphoid follicles (ILFs) are distributed along the length of both the small and large intestines. Compared to the small intestine, the colonic epithelium lacks villi structures and IELs are rarely observed. Paneth cells are typically found only in the small intestine, but are present in the colon during inflammatory conditions. The lamina propria is composed of loose connective tissue traversed by blood vessels, lymphatic vessels, and nerves (not shown), and houses numerous innate and adaptive immune cells. M-cells, macrophages, and dendritic cells (DCs) are responsible for sampling antigens and triggering specific T cell and B cell responses within GALT

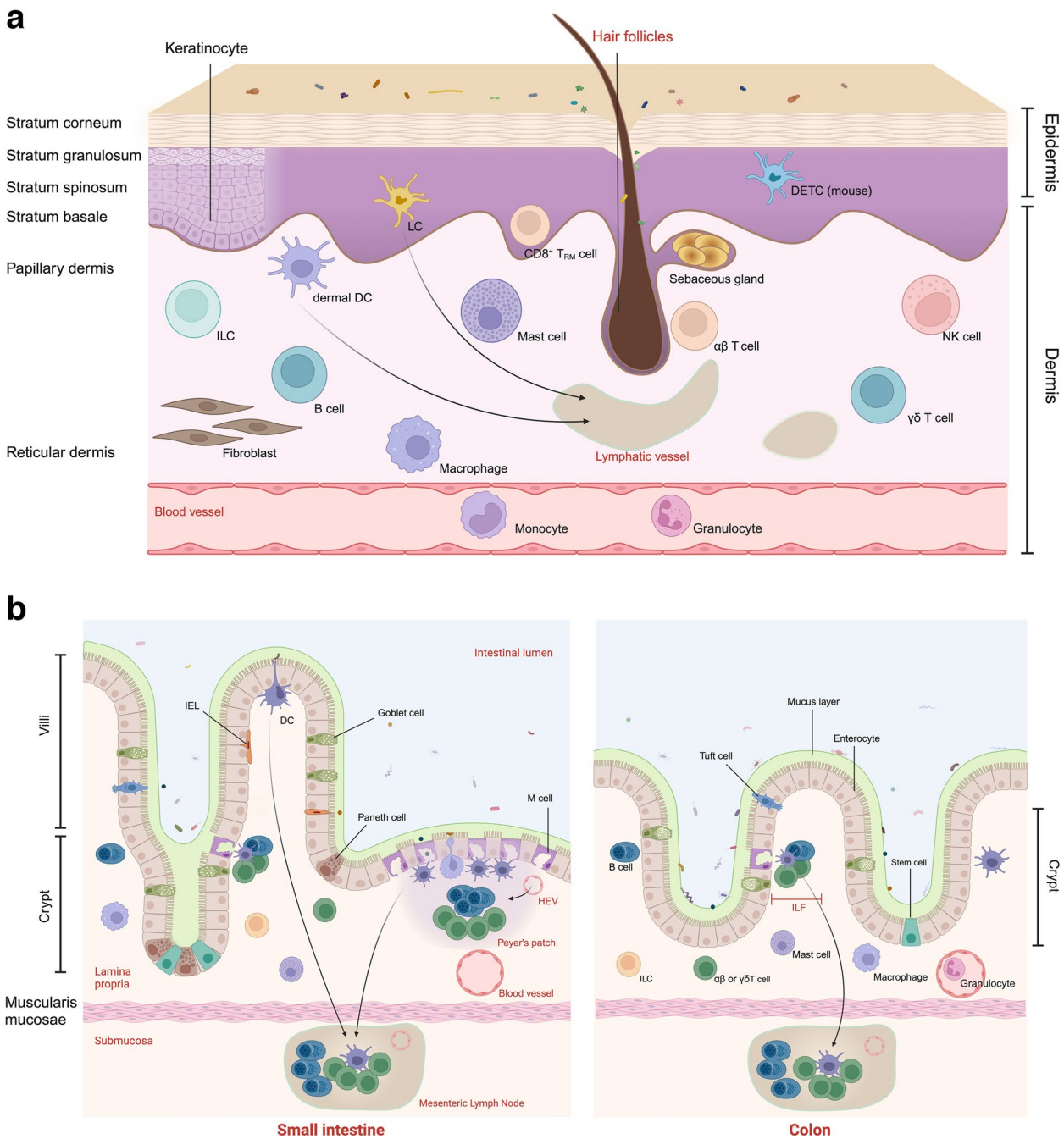

Fig. 2 (See legend on previous page.)

programs biased towards trafficking to associated tissues and microenvironments [96]. There is a hypothesis that each tissue possesses unique "area codes" [62] comprising not only specific combinations of adhesion molecules and chemokines [97], but also environmental cues from sources like food (vitamin A) and sunlight (vitamin D3) in the case of gut and skin, respectively [98].

Retinoic acid (RA), a metabolite of vitamin A, can be produced by intestinal DCs and stromal cells, as well as by the intestinal bacteria [99–101]. When T cells and B cells are activated within GALT, high levels of RA upregulate their expression of gut-homing receptors—$\alpha_4\beta_7$ integrin and CCR9—while concurrently inhibiting the expression of skin-homing receptors, including selectin ligands [102, 103]. MadCAM-1 and CCL25, the ligands

for $\alpha_4\beta_7$ integrin and CCR9, respectively, are almost explicitly expressed in the small intestine and colon [104] (Table 1). Recent studies have revealed that some innate immune cells, including innate lymphoid cells (ILCs) subsets 1 and 3, along with non-classical monocytes [105, 106], can undergo receptor switching that enhances the expression of $\alpha_4\beta_7$ integrin and/or CCR9, through mechanisms like those observed in lymphocytes, thereby acquiring gut-homing phenotypes. It is worth noting that, although the effects of RA are often studied in the context of the gut, RA-producing DCs are not confined to this organ. Specific subsets of DCs derived from extraintestinal barrier tissues also express RA under homeostatic conditions, a feature that corresponds with their ecological niches [107].

The situation for skin-homing leukocytes is more complicated. In humans, vitamin D3 is primarily produced by KCs and fibroblasts in sun-exposed skin [127, 128], and is further metabolized into 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$) by KCs, DCs, and macrophages [129]. $1,25(OH)_2D_3$ has been demonstrated to induce CCR10 expression on antigen experienced T cells [125]. However, other skin-homing receptors, such as CCR8 and CLA, are not induced by $1,25(OH)_2D_3$ but by soluble mediators from KCs during the activation of naive T cells [130]. Interestingly, factors that induce CLA and CCR10, like IL-12 or $1,25(OH)_2D_3$, respectively, can inhibit CCR4 and CCR8 expression [131, 132]. The differential regulation by distinct tissue imprinting factors likely reflects the differing homing requirements of specific lymphocytes subsets, either at steady state or during immune activation [133, 134]. Besides T cells, the expression of skin-homing receptors on human B lymphocytes may also depend on the site of antigenic stimulation [135, 136].

Table 1 Main axes involved in trafficking to skin and gut during health and disease

	Skin		Gut		
	Chemokine pathways	**Adhesion pathways**		**Chemokine pathways**	**Adhesion pathways**
Increased during inflammation					
	CCR2–CCL2 [108] CCR4–CCL17/CCL22 [109] CCR5–CCL5 CCR6–CCL20 CCR8–CCL18 CCR10–CCL27 ?–CCL28 [110] CXCR1/2–CXCL8 [111, 112] CXCR2–CXCL1 CXCR3–CXCL9/CXCL10/CXCL11 [113, 114] CXCR4–CXCL12 CXCR5–CXCL13 CXCR6–CXCL16 [114] CX3CR1–CX3CL1	CLA–E selectin/P selectin CD44–E selectin [115] CD44–hyaluronan L-selectin–PNAd $\alpha_4\beta_1$–VCAM-1 [116] $\alpha_L\beta_2$–ICAM-1 [117] $\alpha_M\beta_2$–ICAM-2 PECAM-1 (CD31) GPR15–GPR15L	Small intestine	CCR2–CCL2/7/8 CCR6–CCL20 CXCR3–CXCL9/10/11 CCR5–CCL3/4/5/8 CX3CR1–CX3CL1	$\alpha_4\beta_7$/L-selectin–MAdCAM-1 $\alpha_4\beta_1$–VCAM-1 $\alpha_L\beta_2$–ICAM-1 VAP-1 E-selectin L-selectin–PNAd PSGL-1–P-selectin
			Colon	CCR2–CCL2/7/8 CCR3–CCL11 CCR4–CCL17 CCR6–CCL20 CCR9–CCL25 CXCR1–CXCL5/6/8 CXCR2–CXCL1/2/5/6/8 CXCR3–CXCL9/10/11	$\alpha_4\beta_7$–MAdCAM-1 [118] L-selectin–PNAd E-selectin
Constitutive expression					
	CCR4–CCL17 [119]/CCL22 [119–121] CCR6–CCL20 [122, 123] CCR8–CCL1 [124] CCR10–CCL27 [125]	CD103–E-cadherin CD69 E selectin [72]	Small intestine	CCR6–CCL20 CCR9–CCL25 CXCR1–CXCL5/6/8 CXCR2–CXCL1/2/5/6 CXCR6–CXCL16 CX3CR1–CX3CL1 CXCR5–BCA-1 (CXCL13)	$\alpha_4\beta_7$–MadCAM-1
			Colon	CCR5–CCL3/4/5/8 CCR6–CCL20 CCR10–CCL28 CX3CR1–CX3CL1 GPR15–GPR15L CXCR5–BCA-1 (CXCL13)	$\alpha_4\beta_7$–MadCAM-1 CD103–E-cadherin

Table is modified from reference [90, 126]

Plasticity in immune cell trafficking along the gut-skin axis

The above-depicted model of issue-specific homing was never meant to be rigid, acknowledging that immune cells can migrate between the gut and skin. The adaptability of this process is partly due to APCs, which modulate the tissue-specific imprinting on immune cells.

The mucosal imprinting capacity of DCs is influenced by the local tissue environment [137]. Under homeostatic conditions, RA signaling promotes gut homing by inducing the expression of ITGA4 and CCR9, which encode the α subunit of $\alpha_4\beta_7$ integrin and CCR9, respectively [138]. Simultaneously, RA suppresses FUT7, a gene that controls CLA/sLe^X expression, which is critical for skin homing. However, this pattern of induction may be disrupted in the presence of inflammatory mediators. Soluble factors from intestinal DCs such as cytokines IL-12/23 may override the suppressive effect of RA on FUT7. These cytokines also enhance the expression of the enzyme C2GlcNAcT-I, pivotal for the formation of P-selectin ligands [139, 140], thereby favoring skin homing [141]. This switch in homing preferences is evidenced by a substantial proportion of activated gut $CD4^+$ T cells expressing both skin and gut homing receptors, as seen in animal models of ileitis or colitis and in cases of human Crohn's disease [141, 142]. These activated gut $CD4^+$ T cells are capable of bidirectional migration between the gut and the skin. Furthermore, antigen dose and strength influence homing receptor expression; high antigen doses presented by murine MLN DCs have been shown to reduce $\alpha_4\beta_7$ and CCR9 expression on effector T cells, curtailing gut infiltration and promoting skin homing [143, 144]. Currently, it is unclear whether the induction of gut homing receptors is effective under inflammatory conditions in the cutaneous environment.

Immune cell trafficking is key in managing disseminated infections, whereby migratory T and B cells can alter their tissue tropism after interacting with tissue-specific DCs and microenvironments [145]. In vitro experiments show that effector-memory T cells initially programmed for gut homing can switch to skin tropism after activation by skin-derived DCs, with corresponding changes in homing receptor expression [146]. Conversely, skin-homing memory T cells can acquire gut homing capabilities following stimulation by intestinal DCs [147]. This flexibility is confirmed in vivo; for example, a subset of $CD8^+$ T cells post-skin infection reorient to express gut-homing molecules after migrating to the MLNs. Preventing their early skin-draining lymph nodes egress with FTY720 (an antagonist of S1PR1) hampers this reprogramming [145]. Additionally, unconventional T cells (UTCs) such as γδ T cells and MR1 or CD1d-restricted T cells [148] may also modulate homing patterns [149]. After migrating to draining lymph nodes, UTCs and DCs contribute to site-specific immunity and prepare the immune system for potential future pathogen encounters [70]. It is notable that effector T cells can also localize to non-infected tissues, suggesting other, as yet unidentified, recruitment mechanisms [150].

It is essential to note the pleiotropy and redundancy inherent in cell trafficking pathways [28] (Table 1). For instance, during intestinal inflammation, the recruitment of inflammatory cells mediated by the non-gut-specific homing receptor $\alpha_4\beta_1$ is crucial for the progression of colitis [151, 152]; its ligand, VCAM-1, is ubiquitously expressed in inflamed tissues [153], which may mediate leukocyte homing to extraintestinal organs.

In summary, immune cells typically exhibit controlled migration patterns, guided by a range of molecules [97]. However, immune dysregulation can lead to aberrant cell migration, potentially exacerbating disease spread. Deviations can occur due to (1) altered imprinting preferences for homing characteristics at their site of activation, (2) reprogramming of homing receptors following encounters with DCs from other tissues, or (3) upregulated expression of gut-specific, skin-specific, or non-specific trafficking molecules by distinct organs. These changes may enable pathogenic immune cells to access distant organs, thus playing a role in disease progression and associated complications [23, 25, 28].

Aberrant immune cell trafficking between the gut and skin

Aberrant skin trafficking of gut-derived cells

Recent studies have provided compelling evidence that aberrant trafficking of gut-derived immune cells to the skin contributes to skin inflammation. Omenn syndrome (OS) is an immunodeficiency disorder characterized by early onset erythroderma, enteritis, and tissue infiltration by overactive T cells [154]. Research indicates that using dextran sulfate sodium (DSS) to aggravate colitis in OS mouse models leads to amplified skin inflammation, with a notable increase in circulating $CD4^+$ T cells expressing both skin- and gut-homing receptors (CCR4 and CCR9) [155]. Concomitantly, serum lipopolysaccharide binding protein (LBP) levels increase, signaling more systemic antigen translocation and inflammation [155, 156]. However, acute systemic inflammation alone does not trigger skin-specific responses, suggesting that a "leaky gut" is key to exacerbating skin inflammation [155, 157]. Further research by Merana et al. implies that gut inflammation can disrupt the skin's adaptive immune tolerance to its normal microbial inhabitants. Typically, the immune systems in the gut and skin operate independently, and fluctuations in the gut microbiota do not directly affect cutaneous immune homeostasis [157]. However, this separation can weaken in cases of inflammation [158,

159]. Experiments have shown that colitis prompts a migration of gut-microbe-responsive $CD4^+$ T cells to skin-associated lymph nodes, increasing skin neutrophils and decreasing Tregs specific to skin microbes, all of which contribute to skin inflammation [160]. Blocking the travel of lymphocytes can re-establish skin immune tolerance, pointing to the gut as the origin of effector cells in skin inflammation. Classon et al.'s findings agree, demonstrated that treating mice with FTY720, which obstructs cell migration from the gut to the skin, resulted in a decreased presence of skin-directed helminth-specific Th2 $CD4^+$ T cells in the context of intestinal helminth infections [161]. Researchers have noted that T cells, which are specific for gut-derived antigens and have migrated from the gastrointestinal tract, are key mediators of skin inflammation. Upon adoptive transfer to naive recipients, these T cells can provoke skin inflammatory responses that are clinically similar to the donor's condition. Conversely, strategies that impede the trafficking of these effector cells—through genetic manipulation or by antagonizing homing receptors—effectively mitigate the inflammation [157, 162].

The reprogramming of homing receptors, a process that takes place in lymph nodes, is currently known to be the primary mechanism of aberrant migration from the gut to skin. Skin-derived DCs that migrate to peripheral lymph nodes are a potential trigger for this reprogramming [155, 162]. Oyoshi et al.'s pivotal study on AD in mice described a mechanism where antigen-specific intestinal homing $CD4^+$ $\alpha_4\beta_7^+$ $CCR4^-$ T cells, primed via oral allergens, undergo reprogramming in mesenteric or peripheral lymph nodes after encountering skin antigens [162]. These cells then migrate to compromised skin sites in a CCR4-dependent manner. Key evidence includes the presence of skin-derived, antigen-bearing DCs in the MLNs following a cutaneous antigen challenge [162]. Additionally, vascular remodeling and enhanced lymphatic clearance appear to influence the peripheral transportation of skin-derived DCs [155]. The production of vitamin D3 by DCs, upregulated by mechanical skin disruptions like scratching in AD, may also play a role in reprogramming [15, 162].

Contrasting the outlined hypothesis, a study utilizing AD mouse models found unique outcomes. T cells, activated via skin or gut by ovalbumin (OVA), were transferred to naive mice followed by OVA skin challenge. Surprisingly, only the cutaneously activated T cells induced AD-like inflammation [163]. This suggests that antigen presentation specifics, such as dose and exposure duration, are critical for effective reprogramming of homing receptors.

Some studies aimed at optimizing vaccination strategies have also provided evidence for the migration of DCs. Transcutaneous immunization (TCI) has proven effective in generating both systemic and mucosal antibody responses, as well as mucosal cytotoxic T lymphocytes (CTL) responses [164], as evidenced in animal models and human trials [165, 166]. One investigation revealed that following TCI with tetanus toxoid (TT) and adjuvant in mice, a substantial number of TT-specific antibody-secreting cells can be detected in the small intestine and colon [167]. Research has identified that the MLNs serve as the inductive sites for intestinal IgA responses following TCI [168]. Another study reported that TCI with an HIV peptide and adjuvant in mice induced HIV-specific CTLs in the gut-associated lymphoid tissue, conferring protection against mucosal viral challenges. Subsequent experiments suggested possible migration of activated DCs carrying skin-derived antigens from the skin to immune-inductive sites within the gut mucosa [164]. Collectively, these findings suggest that the MLN occupies a key position in immune anatomy, bridging the gut and systemic immune systems.

Aberrant gut trafficking of skin-derived cells

Pathogenic immune cells can also traffic aberrantly from the skin to the gut, and the mechanisms of their migration appear to differ from those originating in the gut. Emerging research challenges the notion that tissue-resident memory T cells (TRMs) are confined to their tissue of origin [169]. Instead, these cells may recirculate and contribute to systemic inflammatory conditions like IBD [170–175]. Strobl et al.'s study utilizing allogeneic hematopoietic stem cell transplantation (HSCT) as a model uncovered that patients with active graft-versus-host disease (GVHD) exhibit increased levels of circulating TRMs (cTRMs) with origins in the skin, characterized by a pro-inflammatory Th2/Th17 biased activated phenotype. Notably, these cTRMs express gut-homing receptors and are implicated in gastrointestinal GVHD pathogenesis, as evidenced by their presence in intestinal lesions [176]. This suggests that cTRMs can migrate from skin to the gut, precipitating gastrointestinal inflammatory responses.

To date, the potential of disrupting cell trafficking as a treatment for multi-organ comorbidities remains largely unexplored. Vedolizumab, a selective $\alpha_4\beta_7$ integrin antagonist for IBD treatment [177], has been hypothesized to reduce the severity of cEIMs. This hypothesis rests on the understanding that lymphocytes require the $\alpha_4\beta_7$–MAdCAM1 interaction for gut access and activation, followed by a non-$\alpha_4\beta_7$-dependent pathway for skin entry. Yet, there is a lack of substantial real-world research data to support this. Studies, including case series, cohort studies, and randomized controlled trial analyses, suggest that vedolizumab may alleviate skin conditions such as

pyoderma gangrenosum, erythema nodosum, or aphthous stomatitis in some IBD patients, but not in all [178–180]. Additionally, vedolizumab has been associated with the onset of new arthritis cases and paradoxical skin lesions [181–183]. These complex phenomena could be due to the drug's selective inhibition of gut-homing receptors, which might paradoxically lead to an increased accumulation of pathogenic immune cells at extraintestinal sites, or due to the different underlying pathophysiological mechanisms of various cEIMs. A deeper understanding of cell trafficking between the gut and skin is essential to develop innovative therapeutic strategies in vaccine development, immunotherapy, and anti-adhesion therapies.

Conclusions

The dysregulation of immune cell migration emerges as a contributing factor to the spread of inflammation from primary sites to distant organs. Despite this recognition, critical questions remain unanswered:

1) The specific molecular mechanisms that trigger the reprogramming of homing receptors on immune cells have not been fully characterized.
2) The conditions that precipitate the egress of DCs from local lymph nodes require elucidation.
3) Distinct mechanisms that regulate the recruitment of gut-derived cells to the skin and other extraintestinal locations need to be clarified, highlighting potential differences in these processes [184].

Addressing these fundamental research questions is pivotal for clinical translation. In the realm of clinical applications, research could focus on strategies to induce immune tolerance in the skin to alleviate intestinal inflammation [185] and, conversely, strategies aimed at inducing immune tolerance in the intestines to alleviate cutaneous inflammation. The development of novel vaccination strategies [186, 187] and anti-migratory therapies also holds promise.

Abbreviations

PNAd	Peripheral-node addressin
MAdCAM	Mucosal addressin cell adhesion molecule
ICAM	Intracellular adhesion molecule
VCAM	Vascular cell adhesion molecule
HCAM	Hyaluronate-binding cell adhesion molecule
PSGL	P-selectin glycoprotein ligand
CLA	Cutaneous lymphocyte-associated antigen
VAP	Vascular adhesion protein
PECAM	Platelet-endothelial cell adhesion molecule
JAMs	Junctional adhesion molecules
HEV	High endothelial venule
PP	Peyer's patch
ILF	Isolated lymphoid follicle
MLN	Mesenteric lymph node
IEL	Intestinal intraepithelial lymphocyte
CCR	C-C chemokine receptor
CXCR	C-X-C chemokine receptor
CCL	C-C motif chemokine ligand
CXCL	C-X-C motif chemokine ligand
AD	Atopic dermatitis
GPR	G protein-coupled receptor

Acknowledgements
The figures were created with BioRender.com.

Authors' contributions
J.Z. conceptualized this review; J.Z. wrote the manuscript and designed the figures; Z.Y. provided critical scientific advice and reviewed the manuscript. Z.Y. helped to conceive and supervise the study.

Funding
This work was supported by funds from the Key Program of the National Natural Science Foundation of China (Grant No. 82230106).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 5 February 2024 Accepted: 15 April 2024
Published online: 24 April 2024

References

1. Kim M, Choi KH, Hwang SW, et al. Inflammatory bowel disease is associated with an increased risk of inflammatory skin diseases: a population-based cross-sectional study. J Am Acad Dermatol. 2017;76:40–8.
2. Vide J, Osório F, Costa-Silva M, et al. Cutaneous morbidity among inflammatory bowel disease patients: a cohort study. J Crohns Colitis. 2018;12:442–51.
3. Rogler G, Singh A, Kavanaugh A, et al. Extraintestinal manifestations of inflammatory bowel disease: current concepts, treatment, and implications for disease management. Gastroenterology. 2021;161:1118–32.
4. Wu C-Y, Chang Y-T, Juan C-K, et al. Risk of inflammatory bowel disease in patients with rosacea: results from a nationwide cohort study in Taiwan. J Am Acad Dermatol. 2017;76:911–7.
5. Schneeweiss MC, Kirchgesner J, Wyss R, et al. Occurrence of inflammatory bowel disease in patients with chronic inflammatory skin diseases: a cohort study. Br J Dermatol. 2022;187:692–703.
6. Chen W-T, Chi C-C. Association of hidradenitis suppurativa with inflammatory bowel disease: a systematic review and meta-analysis. JAMA Dermatol. 2019;155:1022–7.
7. Marzano AV, Borghi A, Stadnicki A, et al. Cutaneous manifestations in patients with inflammatory bowel diseases: pathophysiology, clinical features, and therapy. Inflamm Bowel Dis. 2014;20:213–27.
8. Polkowska-Pruszyńska B, Gerkowicz A, Krasowska D. The gut microbiome alterations in allergic and inflammatory skin diseases–an update. J Eur Acad Dermatol Venereol. 2020;34:455–64.
9. Long J, Gu J, Yang J, et al. Exploring the association between gut microbiota and inflammatory skin diseases: a two-sample Mendelian randomization analysis. Microorganisms. 2023;11:2586.

10. Brauckmann V, Nambiar S, Potthoff A, et al. Influence of dietary supplementation of short-chain fatty acid sodium propionate in people living with HIV (PLHIV). J Eur Acad Dermatol Venereol. 2022;36:881–9.
11. Shi Z, Wu X, Wu C-Y, et al. Bile acids improve psoriasiform dermatitis through inhibition of IL-17A expression and CCL20-CCR6–mediated trafficking of T cells. J Investig Dermatol. 2022;142:1381–90 e11.
12. LeBlanc JG, Milani C, De Giori GS, et al. Bacteria as vitamin suppliers to their host: a gut microbiota perspective. Curr Opin Biotechnol. 2013;24:160–8.
13. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. Gut microbes. 2017;8:172–84.
14. Trompette A, Pernot J, Perdijk O, et al. Gut-derived short-chain fatty acids modulate skin barrier integrity by promoting keratinocyte metabolism and differentiation. Mucosal Immunol. 2022;15:908–26.
15. O'Neill CA, Monteleone G, McLaughlin JT, et al. The gut-skin axis in health and disease: a paradigm with therapeutic implications. BioEssays. 2016;38:1167–76.
16. Fang Z, Pan T, Li L, et al. Bifidobacterium longum mediated tryptophan metabolism to improve atopic dermatitis via the gut-skin axis. Gut Microbes. 2022;14:2044723.
17. Dokoshi T, Seidman JS, Cavagnero KJ, et al. Skin inflammation activates intestinal stromal fibroblasts and promotes colitis. J Clin Investig. 2021;131:e147614.
18. Leyva-Castillo J-M, Galand C, Kam C, et al. Mechanical skin injury promotes food anaphylaxis by driving intestinal mast cell expansion. Immunity. 2019;50:1262–75 e4.
19. Venturelli N, Lexmond WS, Ohsaki A, et al. Allergic skin sensitization promotes eosinophilic esophagitis through the IL-33–basophil axis in mice. J Allergy Clin Immunol. 2016;138:1367–80 e5.
20. Haghikia A, Jörg S, Duscha A, et al. Dietary fatty acids directly impact central nervous system autoimmunity via the small intestine. Immunity. 2015;43:817–29.
21. Galván-Peña S, Zhu Y, Hanna BS, et al. A dynamic atlas of immunocyte migration from the gut. Sci Immunol. 2024;9:eadi0672.
22. Grant AJ, Lalor PF, Salmi M, et al. Homing of mucosal lymphocytes to the liver in the pathogenesis of hepatic complications of inflammatory bowel disease. Lancet. 2002;359:150–7.
23. Adams DH, Eksteen B. Aberrant homing of mucosal T cells and extra-intestinal manifestations of inflammatory bowel disease. Nat Rev Immunol. 2006;6:244–51.
24. Salmi M, Jalkanen S. Human leukocyte subpopulations from inflamed gut bind to joint vasculature using distinct sets of adhesion molecules. J Immunol. 2001;166:4650–7.
25. Hedin C, Vavricka S, Stagg A, et al. The pathogenesis of extraintestinal manifestations: implications for IBD research, diagnosis, and therapy. J Crohns Colitis. 2019;13:541–54.
26. Mueller SN. Neural control of immune cell trafficking. J Exp Med. 2022;219:e20211604.
27. Von Andrian UH, Mackay CR. T-cell function and migration—two sides of the same coin. N Engl J Med. 2000;343:1020–34.
28. Zundler S, Günther C, Kremer AE, et al. Gut immune cell trafficking: inter-organ communication and immune-mediated inflammation. Nat Rev Gastroenterol Hepatol. 2023;20:50–64.
29. Butcher EC, Picker LJ. Lymphocyte homing and homeostasis. Science. 1996;272:60–7.
30. Cinamon G, Shinder V, Alon R. Shear forces promote lymphocyte migration across vascular endothelium bearing apical chemokines. Nat Immunol. 2001;2:515–22.
31. Scheele JS, Marks RE, Boss GR. Signaling by small GTPases in the immune system. Immunol Rev. 2007;218:92–101.
32. Lagarrigue F, Kim C, Ginsberg MH. The Rap1-RIAM-talin axis of integrin activation and blood cell function. Blood. 2016;128:479–87.
33. Hogg N, Patzak I, Willenbrock F. The insider's guide to leukocyte integrin signalling and function. Nat Rev Immunol. 2011;11:416–26.
34. Sun H, Lagarrigue F, Wang H, et al. Distinct integrin activation pathways for effector and regulatory T cell trafficking and function. J Exp Med. 2021;218:e20201524.
35. Sun H, Lagarrigue F, Gingras AR, et al. Transmission of integrin β7 transmembrane domain topology enables gut lymphoid tissue development. J Cell Biol. 2018;217:1453–65.
36. Tweedy L, Thomason PA, Paschke PI, et al. Seeing around corners: cells solve mazes and respond at a distance using attractant breakdown. Science. 2020;369:eaay99792.
37. Lawrence MB, Springer TA. Leukocytes roll on a selectin at physiologic flow rates: distinction from and prerequisite for adhesion through integrins. Cell. 1991;65:859–73.
38. Zhang F, Xu Z, Jolly KJ. Myeloid cell-mediated drug delivery: from nanomedicine to cell therapy. Adv Drug Deliv Rev. 2023;197:114827.
39. Moreau JM, Gouirand V, Rosenblum MD. T-cell adhesion in healthy and inflamed skin. JID Innovations. 2021;1:100014.
40. Kinashi T. Intracellular signalling controlling integrin activation in lymphocytes. Nat Rev Immunol. 2005;5:546–59.
41. Shimonaka M, Katagiri K, Nakayama T, et al. Rap1 translates chemokine signals to integrin activation, cell polarization, and motility across vascular endothelium under flow. J Cell Biol. 2003;161:417–27.
42. Luster AD, Alon R, von Andrian UH. Immune cell migration in inflammation: present and future therapeutic targets. Nat Immunol. 2005;6:1182–90.
43. Feyaerts D, Urbschat C, Gaudillière B, et al. Establishment of tissue-resident immune populations in the fetus. Semin Immunopathol. 2022;44:747–66.
44. Park J-E, Jardine L, Gottgens B, et al. Prenatal development of human immunity. Science. 2020;368:600–3.
45. Gray JI, Farber DL. Tissue-resident immune cells in humans. Annu Rev Immunol. 2022;40:195–220.
46. Chen H, Qin Y, Chou M, et al. Transmembrane protein CD69 acts as an S1PR1 agonist. Elife. 2023;12:e88204.
47. Rosen H, Stevens RC, Hanson M, et al. Sphingosine-1-phosphate and its receptors: structure, signaling, and influence. Annu Rev Biochem. 2013;82:637–62.
48. Matloubian M, Lo CG, Cinamon G, et al. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature. 2004;427:355–60.
49. Fung HY, Teryek M, Lemenze AD, et al. CD103 fate mapping reveals that intestinal CD103− tissue-resident memory T cells are the primary responders to secondary infection. Sci Immunol. 2022;7:eab19925.
50. Sheridan BS, Pham Q-M, Lee Y-T, et al. Oral infection drives a distinct population of intestinal resident memory CD8+ T cells with enhanced protective function. Immunity. 2014;40:747–57.
51. Melssen MM, Lindsay RS, Stasiak K, et al. Differential expression of CD49a and CD49b determines localization and function of tumor-infiltrating CD8+ T cells. Cancer Immunol Res. 2021;9:583–97.
52. Cheuk S, Schlums H, Serezal IG, et al. CD49a expression defines tissue-resident CD8+ T cells poised for cytotoxic function in human skin. Immunity. 2017;46:287–300.
53. Cooper GE, Mayall J, Donovan C, et al. Antiviral responses of tissue-resident CD49a+ lung natural killer cells are dysregulated in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2023;207:553–65.
54. Kang SS, Herz J, Kim JV, et al. Migration of cytotoxic lymphocytes in cell cycle permits local MHC I–dependent control of division at sites of viral infection. J Exp Med. 2011;208:747–59.
55. Takamura S. Impact of multiple hits with cognate antigen on memory CD8+ T-cell fate. Int Immunol. 2020;32:571–81.
56. Mcheik S, Van Eeckhout N, De Poorter C, et al. Coexpression of CCR7 and CXCR4 during B cell development controls CXCR4 responsiveness and bone marrow homing. Front Immunol. 2019;10:2970.
57. Förster R, Davalos-Misslitz AC, Rot A. CCR7 and its ligands: balancing immunity and tolerance. Nat Rev Immunol. 2008;8:362–71.
58. Arasa J, Collado-Diaz V, Halin C. Structure and immune function of afferent lymphatics and their mechanistic contribution to dendritic cell and T cell trafficking. Cells. 2021;10:1269.
59. Masopust D, Soerens AG. Tissue-resident T cells and other resident leukocytes. Annu Rev Immunol. 2019;37:521–46.
60. Weisberg SP, Ural BB, Farber DL. Tissue-specific immunity for a changing world. Cell. 2021;184:1517–29.
61. Jalkanen S, Salmi M. Lymphatic endothelial cells of the lymph node. Nat Rev Immunol. 2020;20:566–78.
62. Masopust D, Schenkel JM. The integration of T cell migration, differentiation and function. Nat Rev Immunol. 2013;13:309–20.

63. Blair TC, Alice AF, Zebertavage L, et al. The dynamic entropy of tumor immune infiltrates: the impact of recirculation, antigen-specific interactions, and retention on T cells in tumors. Front Oncol. 2021;11:653625.
64. Yamada KM, Sixt M. Mechanisms of 3D cell migration. Nat Rev Mol Cell Biol. 2019;20:738–52.
65. SenGupta S, Parent CA, Bear JE. The principles of directed cell migration. Nat Rev Mol Cell Biol. 2021;22:529–47.
66. Nielsen MM, Witherden DA, Havran WL. γδ T cells in homeostasis and host defence of epithelial barrier tissues. Nat Rev Immunol. 2017;17:733–45.
67. Kobayashi T, Naik S, Nagao K. Choreographing immunity in the skin epithelial barrier. Immunity. 2019;50:552–65.
68. Kabashima K, Honda T, Ginhoux F, et al. The immunological anatomy of the skin. Nat Rev Immunol. 2019;19:19–30.
69. Worbs T, Hammerschmidt SI, Förster R. Dendritic cell migration in health and disease. Nat Rev Immunol. 2017;17:30–48.
70. Ho AW, Kupper TS. T cells and the skin: from protective immunity to inflammatory skin disorders. Nat Rev Immunol. 2019;19:490–502.
71. Dijkgraaf FE, Matos TR, Hoogenboezem M, et al. Tissue patrol by resident memory CD8+ T cells in human skin. Nat Immunol. 2019;20:756–64.
72. Egbuniwe IU, Karagiannis SN, Nestle FO, et al. Revisiting the role of B cells in skin immune surveillance. Trends Immunol. 2015;36:102–11.
73. Nguyen AV, Soulika AM. The dynamics of the skin's immune system. Int J Mol Sci. 2019;20:1811.
74. Azkanaz M, Corominas-Murtra B, Ellenbroek SI, et al. Retrograde movements determine effective stem cell numbers in the intestine. Nature. 2022;607:548–54.
75. van Konijnenburg DPH, Reis BS, Pedicord VA, et al. Intestinal epithelial and intraepithelial T cell crosstalk mediates a dynamic response to infection. Cell. 2017;171:783–94 e13.
76. Correa-Gallegos D, Jiang D, Rinkevich Y. Fibroblasts as confederates of the immune system. Immunol Rev. 2021;302:147–62.
77. Belkaid Y, Tamoutounour S. The influence of skin microorganisms on cutaneous immunity. Nat Rev Immunol. 2016;16:353–66.
78. Zhang C, Merana GR, Harris-Tryon T, et al. Skin immunity: dissecting the complex biology of our body's outer barrier. Mucosal Immunol. 2022;15:551–61.
79. Nestle FO, Di Meglio P, Qin J-Z, et al. Skin immune sentinels in health and disease. Nat Rev Immunol. 2009;9:679–91.
80. Klechevsky E, Morita R, Liu M, et al. Functional specializations of human epidermal Langerhans cells and CD14+ dermal dendritic cells. Immunity. 2008;29:497–510.
81. Wang H, Xu J, Xiang L. Microneedle-mediated transcutaneous immunization: potential in nucleic acid vaccination. Adv Healthcare Mater. 2023;12:2300339.
82. Blume-Peytavi U, Vogt A. Human hair follicle: reservoir function and selective targeting. Br J Dermatol. 2011;165:13–7.
83. Christoph T, Müller-Röver S, Audring H, et al. The human hair follicle immune system: cellular composition and immune privilege. Br J Dermatol. 2000;142:862–73.
84. Schittek B, Hipfel R, Sauer B, et al. Dermcidin: a novel human antibiotic peptide secreted by sweat glands. Nat Immunol. 2001;2:1133–7.
85. Lovászi M, Szegedi A, Zouboulis CC, et al. Sebaceous-immunobiology is orchestrated by sebum lipids. Dermato-Endocrinol. 2017;9:e1375636.
86. Mörbe UM, Jørgensen PB, Fenton TM, et al. Human gut-associated lymphoid tissues (GALT); diversity, structure, and function. Mucosal Immunol. 2021;14:793–802.
87. Hu Y, Hu Q, Li Y, et al. γδ T cells: origin and fate, subsets, diseases and immunotherapy. Signal Transduct Target Ther. 2023;8:434.
88. Veldhoen M, Brucklacher-Waldert V. Dietary influences on intestinal immunity. Nat Rev Immunol. 2012;12:696–708.
89. Viola MF, Boeckxstaens G. Niche-specific functional heterogeneity of intestinal resident macrophages. Gut. 2021;70:1383–95.
90. Monasterio G, Castillo FA, Villablanca EJ. Leukocyte trafficking to the intestinal barrier in health and disease. In: Schnoor M, Yin L-M, Sun SX, editors. Cell movement in health and disease. Academic Press; 2022. p. 203–35.
91. Brandtzaeg P, Kiyono H, Pabst R, et al. Terminology: nomenclature of mucosa-associated lymphoid tissue. Mucosal Immunol. 2008;1:31–7.
92. Sun T, Nguyen A, Gommerman JL. Dendritic cell subsets in intestinal immunity and inflammation. J Immunol. 2020;204:1075–83.
93. Macpherson AJ, Uhr T. Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. Science. 2004;303:1662–5.
94. Liu J, Zhang X, Cheng Y, et al. Dendritic cell migration in inflammation and immunity. Cell Mol Immunol. 2021;18:2461–71.
95. McGhee JR, Fujihashi K. Inside the mucosal immune system. PLoS Biol. 2012;10:e1001397.
96. Kunkel EJ, Butcher EC. Chemokines and the tissue-specific migration of lymphocytes. Immunity. 2002;16:1–4.
97. Fowell DJ, Kim M. The spatio-temporal control of effector T cell migration. Nat Rev Immunol. 2021;21:582–96.
98. Sigmundsdottir H, Butcher EC. Environmental cues, dendritic cells and the programming of tissue-selective lymphocyte trafficking. Nat Immunol. 2008;9:981–7.
99. Hammerschmidt SI, Ahrendt M, Bode U, et al. Stromal mesenteric lymph node cells are essential for the generation of gut-homing T cells in vivo. J Exp Med. 2008;205:2483–90.
100. Woo V, Eshleman EM, Hashimoto-Hill S, et al. Commensal segmented filamentous bacteria-derived retinoic acid primes host defense to intestinal infection. Cell Host Microbe. 2021;29:1744–56 e5.
101. Cao YG, Bae S, Villarreal J, et al. Faecalibaculum rodentium remodels retinoic acid signaling to govern eosinophil-dependent intestinal epithelial homeostasis. Cell Host Microbe. 2022;30:1295–310 e8.
102. Iwata M, Hirakiyama A, Eshima Y, et al. Retinoic acid imprints gut-homing specificity on T cells. Immunity. 2004;21:527–38.
103. Mora JR, Iwata M, Eksteen B, et al. Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. Science. 2006;314:1157–60.
104. Briskin M, Winsor-Hines D, Shyjan A, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. Am J Pathol. 1997;151:97.
105. Kim MH, Taparowsky EJ, Kim CH. Retinoic acid differentially regulates the migration of innate lymphoid cell subsets to the gut. Immunity. 2015;43:107–19.
106. Schleier L, Wiendl M, Heidbreder K, et al. Non-classical monocyte homing to the gut via α4β7 integrin mediates macrophage-dependent intestinal wound healing. Gut. 2020;69:252–63.
107. Guilliams M, Crozat K, Henri S, et al. Skin-draining lymph nodes contain dermis-derived CD103− dendritic cells that constitutively produce retinoic acid and induce Foxp3+ regulatory T cells. Blood. 2010;115:1958–68.
108. Shibuya R, Ishida Y, Hanakawa S, et al. CCL2-CCR2 signaling in the skin drives surfactant-induced irritant contact dermatitis through IL-1β-mediated neutrophil accumulation. J Investig Dermatol. 2022;142:571–82 e9.
109. Matsuo K, Nagakubo D, Komori Y, et al. CCR4 is critically involved in skin allergic inflammation of BALB/c mice. J Investig Dermatol. 2018;138:1764–73.
110. Kagami S, Kakinuma T, Saeki H, et al. Increased serum CCL28 levels in patients with atopic dermatitis, psoriasis vulgaris and bullous pemphigoid. J Invest Dermatol. 2005;124:1088–90.
111. Ha H, Debnath B, Neamati N. Role of the CXCL8-CXCR1/2 axis in cancer and inflammatory diseases. Theranostics. 2017;7:1543.
112. Cambier S, Gouwy M, Proost P. The chemokines CXCL8 and CXCL12: molecular and functional properties, role in disease and efforts towards pharmacological intervention. Cell Mol Immunol. 2023;20:217–51.
113. Mabuchi T, Chang TW, Quinter S, et al. Chemokine receptors in the pathogenesis and therapy of psoriasis. J Dermatol Sci. 2012;65:4–11.
114. Speeckaert R, Belpaire A, Speeckaert MM, et al. A meta-analysis of chemokines in vitiligo: recruiting immune cells towards melanocytes. Front Immunol. 2023;14:1112811.
115. Dimitroff CJ, Lee JY, Rafii S, et al. CD44 is a major E-selectin ligand on human hematopoietic progenitor cells. J Cell Biol. 2001;153:1277–86.
116. Czarnowicki T, Santamaria-Babí L, Guttman-Yassky E. Circulating CLA+ T cells in atopic dermatitis and their possible role as peripheral biomarkers. Allergy. 2017;72:366–72.
117. Koch S, Kohl K, Klein E, et al. Skin homing of Langerhans cell precursors: adhesion, chemotaxis, and migration. J Allergy Clin Immunol. 2006;117:163–8.

118. Rivera-Nieves J, Olson T, Bamias G, et al. L-selectin, α4β1, and α4β7 integrins participate in CD4+ T cell recruitment to chronically inflamed small intestine. J Immunol. 2005;174:2343–52.
119. Campbell J, Haraldsen G, Pan J, et al. The chemokine receptor CCR4 in vascular recognition by cutaneous but not intestinal memory T cells. Nature. 1999;400:776–80.
120. Ferenczi K, Fuhlbrigge RC, Kupper TS, et al. Increased CCR4 expression in cutaneous T cell lymphoma. J Investig Dermatol. 2002;119:1405–10.
121. Munoz LD, Sweeney MJ, Jameson JM. Skin resident γδ T cell function and regulation in wound repair. Int J Mol Sci. 2020;21:9286.
122. Harper EG, Guo C, Rizzo H, et al. Th17 cytokines stimulate CCL20 expression in keratinocytes in vitro and in vivo: implications for psoriasis pathogenesis. J Investig Dermatol. 2009;129:2175–83.
123. Liu N, Qin H, Cai Y, et al. Dynamic trafficking patterns of IL-17-producing γδ T cells are linked to the recurrence of skin inflammation in psoriasis-like dermatitis. EBioMedicine. 2022;82:104136.
124. Schaerli P, Ebert L, Willimann K, et al. A skin-selective homing mechanism for human immune surveillance T cells. J Exp Med. 2004;199:1265–75.
125. Sigmundsdottir H, Pan J, Debes GF, et al. DCs metabolize sunlight-induced vitamin D3 to 'program' T cell attraction to the epidermal chemokine CCL27. Nat Immunol. 2007;8:285–93.
126. Eksteen B, Liaskou E, Adams DH. Lymphocyte homing and its role in the pathogenesis of IBD. Inflamm Bowel Dis. 2008;14:1298–312.
127. Mostafa WZ, Hegazy RA. Vitamin D and the skin: focus on a complex relationship: a review. J Adv Res. 2015;6:793–804.
128. Sawicki K, Czajka M, Matysiak-Kucharek M, et al. Chlorpyrifos alters expression of enzymes involved in vitamin D3 synthesis in skin cells. Pestic Biochem Physiol. 2021;174:104812.
129. Schön MP, Zollner TM, Boehncke W-H. The molecular basis of lymphocyte recruitment to the skin: clues for pathogenesis and selective therapies of inflammatory disorders. J Investig Dermatol. 2003;121:951–62.
130. McCully ML, Ladell K, Hakobyan S, et al. Epidermis instructs skin homing receptor expression in human T cells. Blood. 2012;120:4591–8.
131. Ebel ME, Awe O, Kaplan MH, et al. Diverse inflammatory cytokines induce selectin ligand expression on murine CD4 T cells via p38α MAPK. J Immunol. 2015;194:5781–8.
132. Reiss Y, Proudfoot AE, Power CA, et al. CC chemokine receptor (CCR) 4 and the CCR10 ligand cutaneous T cell–attracting chemokine (CTACK) in lymphocyte trafficking to inflamed skin. J Exp Med. 2001;194:1541–7.
133. McCully ML, Ladell K, Andrews R, et al. CCR8 expression defines tissue-resident memory T cells in human skin. J Immunol. 2018;200:1639–50.
134. Vu TT, Koguchi-Yoshioka H, Watanabe R. Skin-resident memory t cells: pathogenesis and implication for the treatment of psoriasis. J Clin Med. 2021;10:3822.
135. Sundström P, Lundin SB, Nilsson LÅ, et al. Human IgA-secreting cells induced by intestinal, but not systemic, immunization respond to CCL25 (TECK) and CCL28 (MEC). Eur J Immunol. 2008;38:3327–38.
136. Kantele A, Savilahti E, Tiimonen H, et al. Cutaneous lymphocyte antigen expression on human effector B cells depends on the site and on the nature of antigen encounter. Eur J Immunol. 2003;33:3275–83.
137. Hart AL, Ng SC, Mann E, et al. Homing of immune cells: role in homeostasis and intestinal inflammation. Inflamm Bowel Dis. 2010;16:1969–77.
138. Campbell DJ, Butcher EC. Rapid acquisition of tissue-specific homing phenotypes by CD4+ T cells activated in cutaneous or mucosal lymphoid tissues. J Exp Med. 2002;195:135–41.
139. Schroeter MF, Ratsch BA, Lehmann J, et al. Differential regulation and impact of fucosyltransferase VII and core 2 β1, 6-N-acetyl-glycosaminyl-transferase for generation of E-selectin and P-selectin ligands in murine CD 4+ T cells. Immunology. 2012;137:294–304.
140. Wagers AJ, Waters CM, Stoolman LM, et al. Interleukin 12 and interleukin 4 control T cell adhesion to endothelial selectins through opposite effects on α1, 3-fucosyltransferase VII gene expression. J Exp Med. 1998;188:2225–31.
141. Gordon H, Wichmann K, Lewis A, et al. Human intestinal dendritic cells can overcome retinoic acid signaling to generate proinflammatory CD4 T cells with both gut and skin homing properties. J Immunol. 2023;212:96–106.
142. Hoffmann U, Pink M, Lauer U, et al. Regulation and migratory role of P-selectin ligands during intestinal inflammation. PLoS ONE. 2013;8:e62055.
143. Svensson M, Johansson-Lindbom B, Zapata F, et al. Retinoic acid receptor signaling levels and antigen dose regulate gut homing receptor expression on CD8+ T cells. Mucosal Immunol. 2008;1:38–48.
144. Román E, Miller E, Harmsen A, et al. CD4 effector T cell subsets in the response to influenza: heterogeneity, migration, and function. J Exp Med. 2002;196:957–68.
145. Liu L, Fuhlbrigge RC, Karibian K, et al. Dynamic programing of CD8+ T cell trafficking after live viral immunization. Immunity. 2006;25:511–20.
146. Mora JR, Cheng G, Picarella D, et al. Reciprocal and dynamic control of CD8 T cell homing by dendritic cells from skin-and gut-associated lymphoid tissues. J Exp Med. 2005;201:303–16.
147. Dudda JC, Lembo A, Bachtanian E, et al. Dendritic cells govern induction and reprogramming of polarized tissue-selective homing receptor patterns of T cells: important roles for soluble factors and tissue microenvironments. Eur J Immunol. 2005;35:1056–65.
148. Pellicci DG, Koay H-F, Berzins SP. Thymic development of unconventional T cells: how NKT cells, MAIT cells and γδ T cells emerge. Nat Rev Immunol. 2020;20:756–70.
149. Ataide MA, Knöpper K, de Casas PC, et al. Lymphatic migration of unconventional T cells promotes site-specific immunity in distinct lymph nodes. Immunity. 2022;55:1813–28 e9.
150. Shin H, Iwasaki A. Tissue-resident memory T cells. Immunol Rev. 2013;255:165–81.
151. Soriano A, Salas A, Salas A, et al. VCAM-1, but not ICAM-1 or MAdCAM-1, immunoblockade ameliorates DSS-induced colitis in mice. Lab Invest. 2000;80:1541–51.
152. Zundler S, Fischer A, Schillinger D, et al. The α4β1 homing pathway is essential for ileal homing of Crohn's disease effector T cells in vivo. Inflamm Bowel Dis. 2017;23:379–91.
153. Dotan I, Allez M, Danese S, et al. The role of integrins in the pathogenesis of inflammatory bowel disease: approved and investigational anti-integrin therapies. Med Res Rev. 2020;40:245–62.
154. Villa A, Notarangelo LD, Roifman CM. Omenn syndrome: inflammation in leaky severe combined immunodeficiency. J Allergy Clin Immunol. 2008;122:1082–6.
155. Rigoni R, Fontana E, Dobbs K, et al. Cutaneous barrier leakage and gut inflammation drive skin disease in Omenn syndrome. J Allergy Clin Immunol. 2020;146:1165–79 e11.
156. Eichele DD, Kharbanda KK. Dextran sodium sulfate colitis murine model: an indispensable tool for advancing our understanding of inflammatory bowel diseases pathogenesis. World J Gastroenterol. 2017;23:6016.
157. Merana GR, Dwyer LR, Dhariwala MO et al. Intestinal inflammation alters the antigen-specific immune response to a skin commensal. Cell reports. 2022;39:795–809.e5.
158. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? Nat Rev Immunol. 2021;21:739–51.
159. Hand TW, Dos Santos LM, Bouladoux N, et al. Acute gastrointestinal infection induces long-lived microbiota-specific T cell responses. Science. 2012;337:1553–6.
160. Weckel A, Dhariwala MO, Ly K et al. Long-term tolerance to skin commensals is established neonatally through a specialized dendritic cell subgroup. Immunity. 2023;56:1239–54.e7.
161. Classon CH, Li M, Clavero AL, et al. Intestinal helminth infection transforms the CD4+ T cell composition of the skin. Mucosal Immunol. 2022;15:257–67.
162. Oyoshi MK, Elkhal A, Scott JE, et al. Epicutaneous challenge of orally immunized mice redirects antigen-specific gut-homing T cells to the skin. J Clin Investig. 2011;121:2210–20.
163. Glocova I, Brück J, Geisel J, et al. Induction of skin-pathogenic Th22 cells by epicutaneous allergen exposure. J Dermatol Sci. 2017;87:268–77.
164. Belyakov IM, Hammond SA, Ahlers JD, et al. Transcutaneous immunization induces mucosal CTLs and protective immunity by migration of primed skin dendritic cells. J Clin Investig. 2004;113:998–1007.
165. Ferber S, Gonzalez RJ, Cryer AM, et al. Immunology-guided biomaterial design for mucosal cancer vaccines. Adv Mater. 2020;32:1903847.
166. Bhuiyan MS, Kalsy A, Arifuzzaman M, et al. Transcutaneous vaccination with conjugate typhoid vaccine Vi-DT induces systemic, mucosal, and memory anti-polysaccharide responses. Am J Trop Med Hyg. 2020;103:1032.

167. Chang S-Y, Cha H-R, Igarashi O, et al. Cutting edge: langerin+ dendritic cells in the mesenteric lymph node set the stage for skin and gut immune system cross-talk. J Immunol. 2008;180:4361–5.
168. Chang SY, Kweon MN. Langerin-expressing dendritic cells in gut-associated lymphoid tissues. Immunol Rev. 2010;234:233–46.
169. Schenkel JM, Masopust D. Tissue-resident memory T cells. Immunity. 2014;41:886–97.
170. Chen L, Shen Z. Tissue-resident memory T cells and their biological characteristics in the recurrence of inflammatory skin disorders. Cell Mol Immunol. 2020;17:64–75.
171. Klicznik MM, Morawski PA, Höllbacher B, et al. Human CD4+ CD103+ cutaneous resident memory T cells are found in the circulation of healthy individuals. Sci Immunol. 2019;4:eaav8995.
172. Steinert EM, Schenkel JM, Fraser KA, et al. Quantifying memory CD8 T cells reveals regionalization of immunosurveillance. Cell. 2015;161:737–49.
173. Wijeyesinghe S, Beura LK, Pierson MJ, et al. Expansible residence decentralizes immune homeostasis. Nature. 2021;592:457–62.
174. Fonseca R, Beura LK, Quarnstrom CF, et al. Developmental plasticity allows outside-in immune responses by resident memory T cells. Nat Immunol. 2020;21:412–21.
175. Strobl J, Haniffa M. Functional heterogeneity of human skin-resident memory T cells in health and disease. Immunol Rev. 2023;316:104–19.
176. Strobl J, Gail LM, Kleissl L, et al. Human resident memory T cells exit the skin and mediate systemic Th2-driven inflammation. J Exp Med. 2021;218:e20210417.
177. Colombel J-F, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017;66:839–51.
178. Mader O, Juillerat P, Biedermann L, et al. Factors influencing the outcome of vedolizumab treatment: real-life data with objective outcome measurements. UEG J. 2021;9:398–406.
179. Varkas G, Thevissen K, De Brabanter G, et al. An induction or flare of arthritis and/or sacroiliitis by vedolizumab in inflammatory bowel disease: a case series. Ann Rheum Dis. 2017;76:878–81.
180. Tadbiri S, Peyrin-Biroulet L, Serrero M, et al. Impact of vedolizumab therapy on extra-intestinal manifestations in patients with inflammatory bowel disease: a multicentre cohort study nested in the OBSERV-IBD cohort. Aliment Pharmacol Ther. 2018;47:485–93.
181. Livne-Margolin M, Ling D, Attia-Konyo S, et al. Ustekinumab and vedolizumab for extraintestinal manifestations in inflammatory bowel disease-a retrospective study. Dig Liver Dis. 2023;55:223–9.
182. Hanzel J, Ma C, Casteele NV, et al. Vedolizumab and extraintestinal manifestations in inflammatory bowel disease. Drugs. 2021;81:333–47.
183. Fleisher M, Marsal J, Lee SD, et al. Effects of vedolizumab therapy on extraintestinal manifestations in inflammatory bowel disease. Dig Dis Sci. 2018;63:825–33.
184. Galván-Peña S, Zhu Y, Hanna BS et al. A dynamic atlas of immunocyte migration from the gut. bioRxiv 2022: 2022.11. 16.516757.
185. Schmidt T, Lorenz N, Raker V, et al. Epicutaneous and oral low-zone tolerance protects from colitis in mice. J Investig Dermatol. 2016;136:1831–9.
186. Hammerschmidt SI, Friedrichsen M, Boelter J, et al. Retinoic acid induces homing of protective T and B cells to the gut after subcutaneous immunization in mice. J Clin Investig. 2011;121:3051–61.
187. Lavelle EC, Ward RW. Mucosal vaccines—fortifying the frontiers. Nat Rev Immunol. 2022;22:236–50.

Publisher's Note