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(Not) Home alone: Antigen presenting cell – T Cell communication in barrier tissues

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Priming of T cells by antigen presenting cells (APCs) is essential for T cell fate decisions, enabling T cells to migrate to specific tissues to exert their effector functions. Previously, these interactions were mainly explored using blood-derived cells or animal models. With great advances in single cell RNA-sequencing techniques enabling analysis of tissue-derived cells, it has become clear that subsets of APCs are responsible for priming and modulating heterogeneous T cell effector responses in different tissues. This composition of APCs and T cells in tissues is essential for maintaining homeostasis and is known to be skewed in infection and inflammation, leading to pathological T cell responses. This review highlights the commonalities and differences of T cell priming and subsequent effector function in multiple barrier tissues such as the skin, intestine and female reproductive tract. Further, we provide an overview of how this process is altered during tissue-specific infections which are known to cause chronic inflammation and how this knowledge could be harnessed to modify T cell responses in barrier tissue.

KEYWORDS

skin, T cells, antigen-presenting cells, female reproductive tract, tissue-resident T cells, intestine, barrier tissue

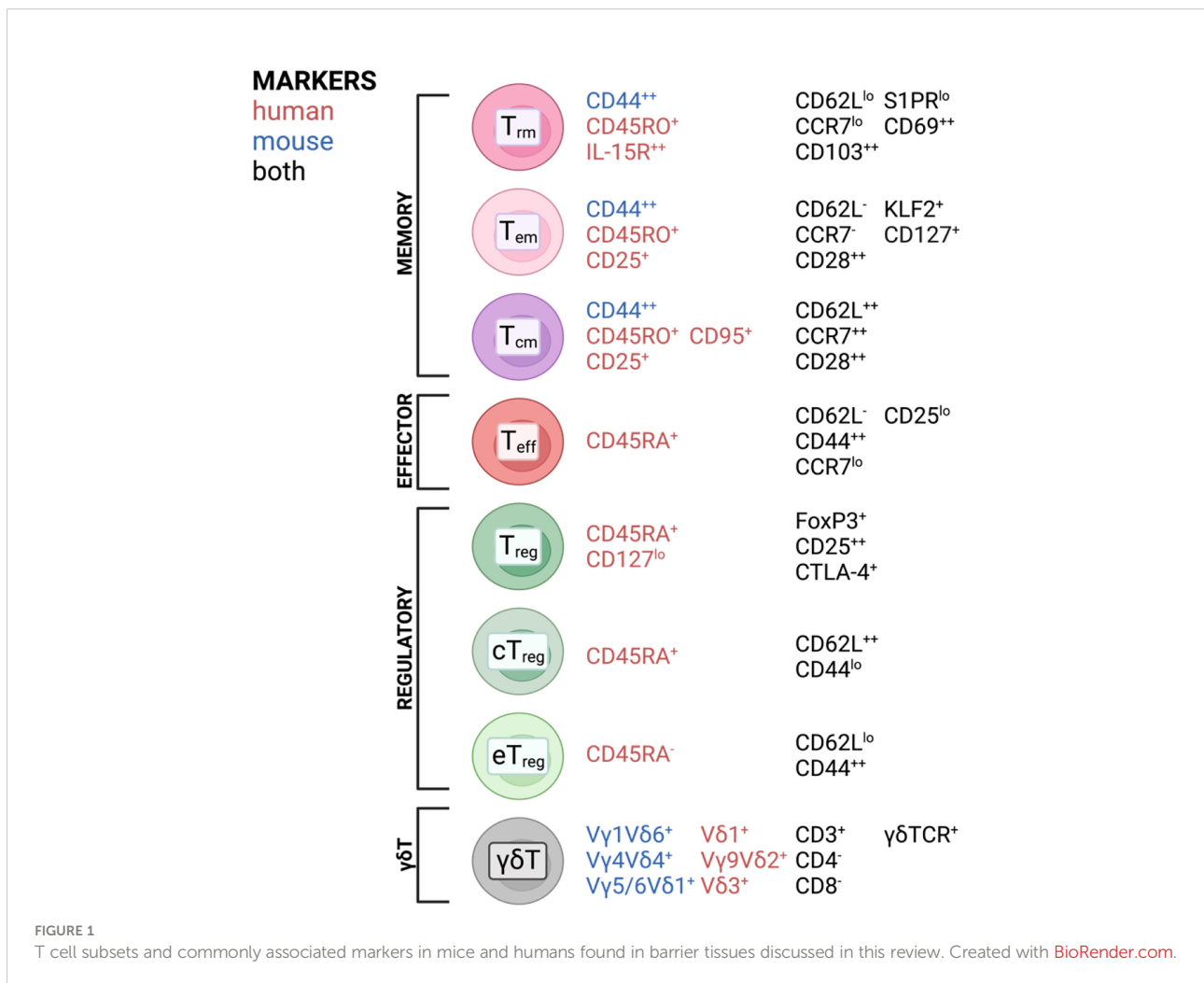
Introduction

T cells are highly specialized executors of immune responses against pathogens and play important roles in maintaining tissue homeostasis. During infection or acute and chronic inflammatory responses, effector T cells (T_{eff}) can infiltrate from the periphery and establish residency and subsequent memory, involving a switch in transcriptional program using different transcription factors and signaling hubs (1–6). This explains why the majority of the T cell population found in tissues are memory T cells

(7), subdivided into central memory T (T_{cm}), effector memory T (T_{em}), and resident memory T (T_{rm}) cells. T_{em} and T_{cm} were first identified in the peripheral blood (8). T_{em} were found to be the predominant subset in non-lymphoid tissue while their T_{cm} counterparts are mainly found in secondary lymphoid organs (9–17). Later, a long-lived memory population with little to no recirculatory capacity was identified and termed T_{rm} (12–18). Another prevalent T cell subset in tissues are regulatory T cells (T_{regs}), particularly important for maintaining a tolerogenic tissue environment, preventing excessive immune responses to harmless antigens often found at barrier tissues [reviewed in (19, 20)]. T_{regs} usually refer to $CD4^+$ T cells with the unique ability to suppress pro-inflammatory effector functions in other T cells as well as contribute to tissue homeostasis (21, 22). Tissue T_{regs} can also be subdivided by the central and effector memory cell classification based on the expression of CD44 and CD62L (23–25), with central T_{regs} being able to recirculate through secondary lymphoid tissues, while effector T_{regs} exhibit a more resident phenotype, representing the predominant T_{reg} population in nonlymphoid tissues (23). Non-conventional T cells can also be found in barrier

tissues. An example of this are $\gamma\delta$ T cells, which are mainly found in epithelial tissues and are particularly abundant in the intestine (26). In homeostatic conditions, $\gamma\delta$ T cells have been described to exhibit a pre-activated memory phenotype (27), being able to exert direct cytotoxic functions (28, 29). As for other T cell subsets in tissues, roles in wound healing and tissue homeostasis have also been attributed to $\gamma\delta$ T cells (30, 31). A broad overview of T cell subsets found in tissues and surface markers most commonly associated with each subset is depicted in Figure 1. It should be noted that these markers are not absolute and their expression is often changed in different tissues. However, these figures aim to give a broad overview over the most common and widely distributed markers of each subset and highlight commonalities and differences between mice and humans.

Priming by antigen presenting cells (APCs) is crucial for T cells to exert their correct functions and home to tissues. For example, the presence and function of T_{regs} in tissue has been directly linked to the presence of dendritic cells (DCs) (32). Tissue-patrolling DCs are of an immature phenotype and internalize antigens by endocytosis or phagocytosis, which are



loaded to major histocompatibility complex class II (MHC-II) for CD4 T cell presentation *via* endosomal pathways (33). However, DCs are also efficient in cross-presenting extracellular antigens *via* MHC-I to CD8 T cells, by which exact mechanism is still under debate (33, 34). Apart from antigen uptake, DCs need to receive additional stimuli in order to mature and upregulate CCR7, by which they interact with the ligands CCL19 and CCL21 guiding them to the lymph nodes to meet naïve T cells (35, 36). Under homeostatic conditions, DCs mainly collect non-hazardous antigens from food or commensal bacteria in the intestinal tract and skin or paternal antigens of fetal cells within the female genital tract during pregnancy (37–39). On the other hand, DCs are highly sensitive against pathogen-associated molecular patterns (PAMPs), which they detect *via* their toll-like receptors or C-type lectin receptors and they sense cytokines produced by other cell types during infection (33, 40). Mature DCs upregulate molecules necessary for co-stimulation of T cells like CD86 and CD80 (41).

Classically, DCs are divided into several subclasses: conventional DCs (cDCs), monocyte-derived DCs (mo-DCs) and plasmacytoid DCs (pDCs) (42). Langerhans cells were previously also classified as DC population; however, they developmentally originate from yolk sac progenitors, which identifies them as member of the tissue-resident macrophage family. In contrast to macrophages, they can efficiently present antigens and possess a migration potential to the lymph node (43). Therefore, they are often mentioned along with other DC subsets inducing T cell responses. Conventional DCs are subdivided into type 1 classical DC (cDC1), which are known to cross-present antigens *via* MHC-I to CD8 T cells but also polarize CD4 T cells towards T_H1, while type 2 classical DCs (cDC2) mainly present antigens *via* MHC-II to CD4 T cells. The cDC1 subset in mice is CD11b^{lo} and shows CD8a and CD103 on their surface, while human cDC1 express and XCR1 and CD141 (33). cDC2 express CD172a and depending on murine or human origin they highly express CD11b or CD1c, respectively (33). Especially cDC2 comprises a very heterogenous immune cell population which can acquire quite contrary immune functions depending on the context. For examples, in human there exists a cDC2 subset which expresses at the same time monocyte-related genes like CD163 and CD14, which was termed DC3 (44, 45). LCs are a population patrolling the epidermis as well as the epithelial layer of the vagina and cervix and are characterized by expression of a specific lectin receptor, langerin (CD207) and CD1a (46). Monocytes express CD14 and can be differentiated *in vitro* to monocyte-derived DCs (mo-DCs) by addition of GM-CSF and IL-4 and are a widely used model for priming T cells *in vitro* (47). However, the existence of mo-DCs *in vivo* remains under debate, but several mouse (48, 49) and human (50) studies observed that monocytes can differentiate into DC-like cells, especially under inflammatory conditions (45, 51). With the evolving of single-cell sequencing technology, more and more

DC subsets are discovered and it now appears that the discrimination between DC and monocyte subsets is not that black and white, with mo-DCs in comparison to DC3 being just one example (44, 45, 52, 53). APC subset composition varies widely throughout tissues and we are still far from understanding which subset contributes to immunity and tolerance under certain conditions (54–57). DCs are in general CD45⁺ cells, expressing HLA-DR and lacking other lineage markers, such as CD3 or CD19 (52). In Figure 2, a simplified overview of the most important DC subsets in human can be found with the markers for those respective subsets in mice included.

In this review, we discuss the different subsets of T cells and APCs present in the skin, intestine and female reproductive tract (FRT) and how their interplay contributes to maintaining a homeostatic tissue environment as well as how this composition shifts during chronic inflammatory diseases and infection. While the term “immune homeostasis” is widely used, we refer to “homeostasis” as the balance between immune activation and suppression in tissues and organs in contribution to maintaining a healthy state of an organism under normal physiological conditions. This review aims to focus on the human system wherever possible; however, some insightful mechanistic studies in different animal models are included as these contribute greatly to our understanding of tissue immunity where human studies are not yet possible. To give a more comprehensive view of already described mechanistic studies not yet discovered in humans we also included animal studies when appropriate. Therefore, unless otherwise stated, findings summarized were done in humans and deviation to animal models is indicated.

Skin

The skin is one of the largest organs in the human body and essential for protection against external injury and pathogens. Next to its role in physical protection, the skin also houses a vast landscape of resident and recirculating immune cells which are poised locally to respond to tissue damage and infection. The skin is comprised of three layers: the outermost epidermis, an intermediate layer termed dermis, and the innermost layer called hypodermis (Figure 3). The epidermis is mainly comprised by structural cells such as keratinocytes, as well as melanocytes. The main immune cells found in this layer are CD8⁺ T cells and LCs, skin-resident macrophages which originate from the fetal liver and the yolk sac, and exhibit DC-like characteristics (58). Next to structural fibroblasts, the dermis contains the majority of immune cells, including DCs, macrophages, natural killer (NK) cells, innate lymphoid cells (ILCs), as well as CD4⁺ and CD8⁺ T cells. Further, this layer is also supplied with lymphatic and blood vessels which allow immune cell trafficking in and out of the tissue. The lowest layer, the hypodermis, is mainly comprised of adipocytes responsible for thermoregulation (59, 60).

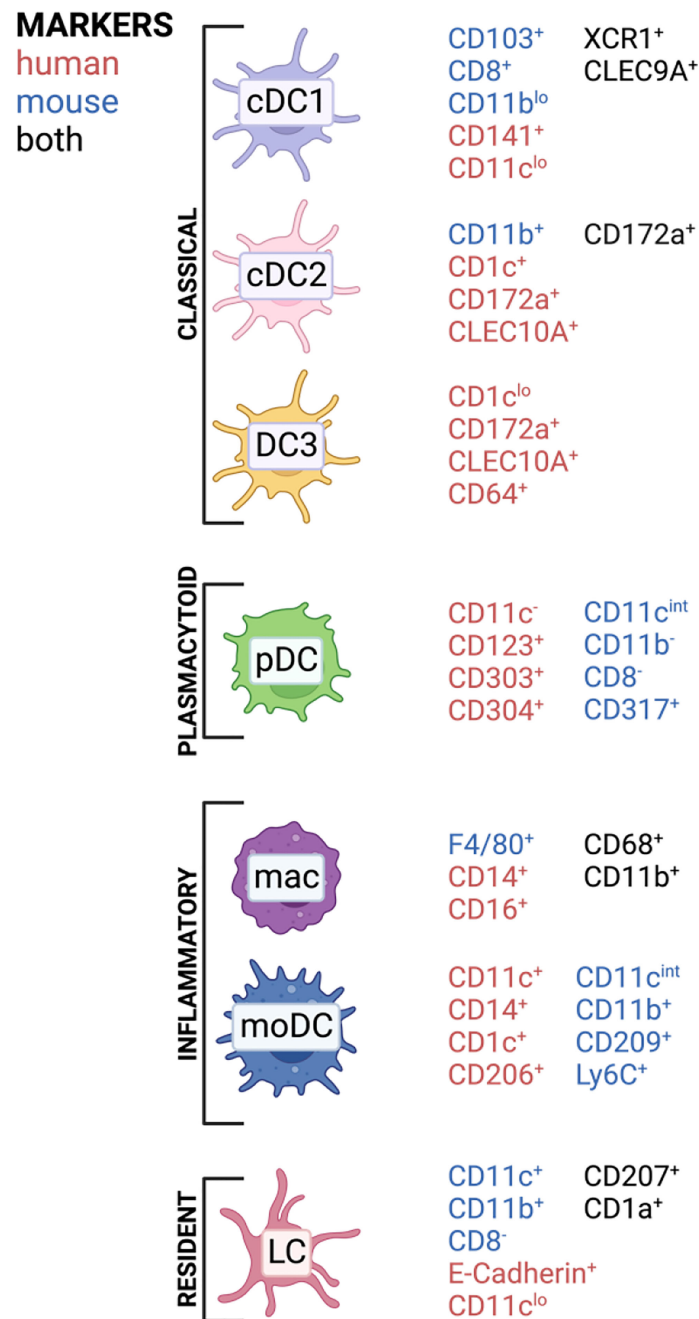
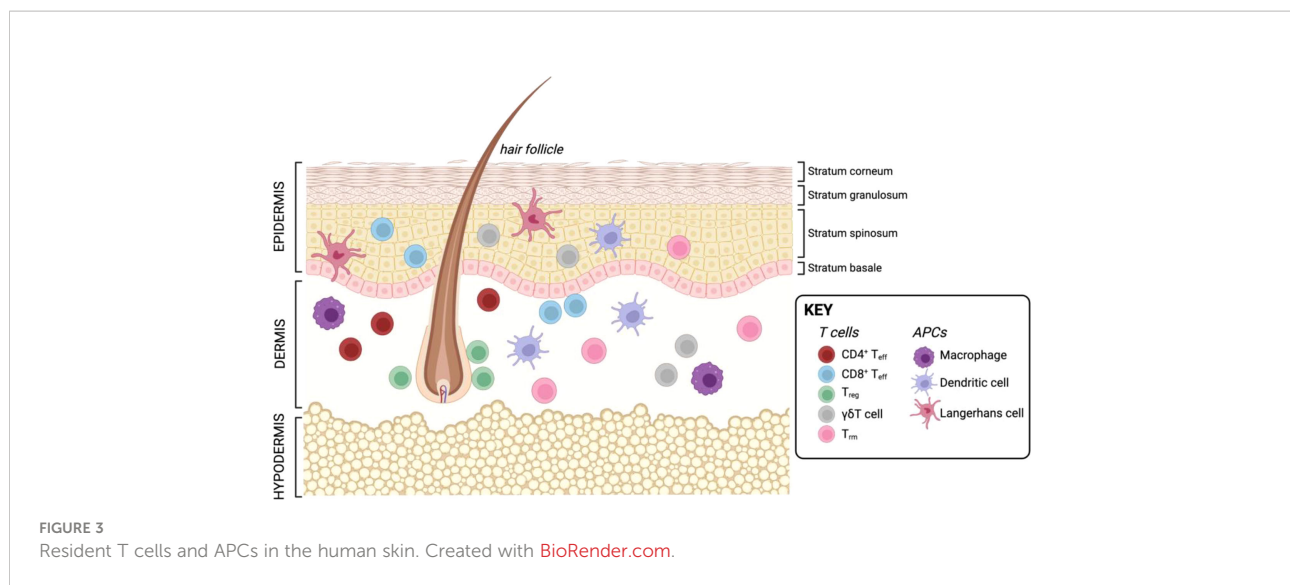


FIGURE 2 APC subsets and commonly associated markers in mice and humans found in barrier tissues discussed in this review. Created with [BioRender.com](https://www.biorender.com).

However, recently an immunological role has been attributed to adipose tissue as it has been shown to house multiple types of immune cells (61–66). Additionally, structures such as hair follicles and nerve endings are major players in regulating immune responses in the skin. Hair follicles represent unique structures in the skin, as many studies in mice have shown that

they are the primary site for T_{reg} maintenance, which are in turn essential for establishing the stem cell niche at the hair follicle (67–69). In human skin, the hair follicle is also the major site of T_{reg} localization (70). Further, the hair follicle is also of importance for DC function in the skin of mice (68, 71). Besides the hair follicle, nerve endings in the skin have been



shown to play an important role for CD8⁺ T cell mediated immunity (72) as well as create a special environment for specific macrophage subsets (73) as demonstrated in mouse models.

Upon encountering pathogens or injury to the epidermal layer, LCs are the first to initiate an immune response. These cells constitute approximately 2–4% of all cells in the epidermis and are specialized macrophages with DC characteristics, expressing the surface markers CD1a and Langerin/CD207 (46), whose dendrites can extend through the stratum corneum to sample antigen without disturbing the epithelial barrier (74, 75). LCs preferentially recognize mannose ligands on surfaces of pathogens via C-type lectins and pattern recognition receptors (PRRs) (76). Binding of these receptors leads to receptor-mediated endocytosis thereby activating the LC (77). Like their conventional DC counterpart, LCs have been found to be able to traffic to the skin-draining lymph nodes (LNs) and activate naïve T cells (78–80) as well as activate skin-resident T_{regs} (81). LCs have also been described to be highly efficient at inducing a neutralizing IgG response against *S. aureus* from B cells (82). While LCs have their primary role in immune surveillance of the skin, macrophages are mainly responsible for initiating inflammatory responses in response to infection or injury as well as to tissue regeneration (83–85).

Apart from the acute role of innate immune cells in clearing infection, APCs also play a major role in activating an adaptive immune response. As in other tissues, dermal APCs expressing CD1c (86, 87) can be divided into multiple subsets. In healthy human skin, the main subsets at steady-state are CD1a⁺⁺CD207⁺ LCs, CD1a⁺CD1c⁺ DCs, CD141⁺⁺CD14⁻ DCs, as well as two populations of macrophages that can be, in part, distinguished by their autofluorescence (AF) created by their high scatter properties: CD14⁺AF⁻ monocyte-derived macrophages (mo-Mac), and FXIII⁺CD14⁺AF⁺⁺ macrophages (88). Upon antigen encounter in the skin, dermal DCs (DDCs) become

migratory and act as APCs in the lymph node where they activate and polarize different adaptive immune cells, such as naïve T cells (88, 89). It was shown in mice that the constant travel of skin APCs to the LN during homeostasis is only dependent on the CCR7 ligand CCL21, whereas CCL19 presence is dispensable for the trafficking (90, 91). However, CCL19 deficient mice exhibit lower T cell numbers due to decreased cell survival (91). However, DCs in the skin have also been shown to locally activate memory T cells within the skin, bypassing the need for tissue egress (81) and thereby enabling a rapid adaptive immune response locally.

Specifically, T cells play a major role in the cutaneous immune system, with a large tissue-resident population being found throughout the dermis and epidermis. In healthy skin, this population can comprise up to 2×10^{10} cells, which is nearly two times as many as found in circulation (17). Differences in T cell composition between murine and human skin have made studies using mouse models difficult. In mice, the majority of resident T cells are $\gamma\delta$ T cells with a limited T cell receptor (TCR) repertoire (92), while in human skin most resident T cells are $\alpha\beta$ T cells with a much greater TCR diversity (17). Overall, T cells in the epidermis are less proliferative but have increased capacity to produce cytokines such as IFN- γ and TNF- α (93). While $\alpha\beta$ T cells rely on antigen presentation via MHC molecules, $\gamma\delta$ T cells have a restricted TCR repertoire, with their receptors recognizing unconventional antigens such as phosphoantigens, stress molecules, as well as non-peptide metabolites (94–96). Human $\gamma\delta$ T cells express the V δ 1, V δ 2, and V δ 3 chains, with each subtype having a preferential distribution across the body (97). A murine-specific $\gamma\delta$ T cell subset, called dendritic epidermal T cells (DETCs), have also been shown to significantly contribute to immune homeostasis in mouse skin (98), but don't have a human counterpart. How different T cells subsets contribute to maintaining homeostasis

and how this paradigm is shifted during the inflammatory response and infection will be discussed below.

DC-T cell composition in homeostasis

Memory T cells

While the T cell subsets above mainly describe different effector states of activated T cells, a central part of T cell function is the capacity to develop long-lived immunological memory. T_{eff} cells primed in the lymph nodes by an APC are maintained in the skin as memory T cells, whose survival is supported by keratinocytes producing growth factors as well as other tissue resident (immune) cells (99, 100). These resident memory cells are crucial for maintaining tissue homeostasis as they contribute to immune surveillance and supply a rapid, specific response when re-encountering pathogens. As with all other immune cell subsets, memory T cells in the skin can be divided into two major groups: resident and recirculating. Using a human skin xenograft model with nude NSG mice, four distinct memory populations in the skin have been identified using the resident vs. recirculating paradigm. In human and mouse skin, the primarily resident subsets are T_{em} and T_{rm} . Recirculating subsets can further be subdivided into migratory memory (T_{mm}) and T_{cm} (8, 93, 101). Cutaneous lymphocyte antigen (CLA) is a marker that specifically distinguishes memory T cells originating from the cutaneous immune system as well as skin-infiltrating T cells. CLA binds to chemokine receptors, E-selectin which together with Very late antigen 1 (VLA-1)/Vascular cell adhesion protein 1 (VCAM-1) and Lymphocyte function-associated antigen 1 (LFA-1)/Intercellular adhesion molecule 1 (ICAM-1) enables skin tropism of these cells (102–105).

T_{em} are thought to be the first responders, expressing high levels of CD44 but lacking migratory and homing receptors such as L-selectin and CCR7 (8, 106, 107), making them incapable of recirculating. As their name suggests, they provide immediate effector function, which is underscored by their production of IFN- γ as well as other pro-inflammatory cytokines (93). While T_{em} are crucial for immediate adaptive responses, this population undergoes significant contraction after an infection is resolved and their niche has been found to be replaced by T_{cm} which enter from the circulation over the course of an acute inflammatory response (13). T_{cm} express high levels of homing receptors that are lacking on T_{em} (CCR7, LCA, CCR4) (17, 108, 109). Contrary to T_{em} , their reactivation primarily takes place in the local LNs. There, they undergo extensive proliferation and adopt a T_{em} -like phenotype (8, 110). The other circulating subset, T_{mm} , was described by Rei et al. (93) and shows a population of cells high in skin-homing receptors such as CLA and CCR7 but are defined by the absence of L-selectin. This lack of L-selectin has raised suspicion that these cells are able to

remain in the skin after infection, where they contribute to immune homeostasis as these cells are not high producers of pro-inflammatory cytokines (93). Another, more recently discovered, family member are T_{rm} which express high levels of the integrin CD103 as well as the glycoprotein CD69. While their overall phenotype is similar to that of T_{em} , they have been shown to be maintained long-term even after an infection, as well as being significantly more potent in their effector response while also being limited in their proliferative capacity (13, 111). An essential tool in understanding the migratory behavior of T_{rm} is two-photon intravital microscopy. Multiple studies in mice have revealed that, in the skin, these cells are relatively stationary and confined in and close to the epidermis where they surveil their environment and are responsible for regulating secondary recall responses after primary challenge (112–114). Together, these memory subsets contribute to long-lasting immune memory and surveillance in the skin.

Effector T cells

While T cells in the skin at steady-state are mostly memory T cells, effector T cells (T_{eff}) can also be found. These are activated by APCs in the skin-draining lymph nodes and traffic to the skin, where they further encounter cutaneous APCs presenting their cognate antigen, which leads to T cell activation and production of effector cytokines (115, 116). Most studies on T_{eff} cells have described essential roles for $CD8^+$ T_{eff} cells in maintaining tissue homeostasis in the skin. $CD8^+$ T cells can be found in both the dermis as well as the epidermis. $CD8^+$ T cells have been shown to have increased migratory capacity within different skin compartments, albeit with slower kinetics than migration in the lymph node (117). In a sophisticated *ex vivo* imaging system of whole skin to observe T cell migration, Dijkgraaf et al., could demonstrate that human $CD8^+$ skin-resident T_{rm} in the epidermis migrate along the stratum basale, close to the basement membrane and preferentially localize below aggregations of stationary LCs. In contrast, $CD8^+$ T cells in the papillary dermis were observed to accumulate in collagen I rich regions as well as collagen I-poor dermal vessels. These observed migration dynamics highlight an important function of $CD8^+$ skin-resident T cells in tissue patrol, possibly enabling immediate cytotoxic response to antigen presentation by co-localized LCs at the epidermal-dermal junction (118). While $CD8^+$ T cell co-localization with LCs at the epidermis-dermis interface may hint at increased priming capacity by local epidermis-patrolling APCs, observed changes in morphology of $CD8^+$ T_{rm} to a more dendrite-like shape (7, 117, 119, 120) could also suggest that these memory cells can act, at least in part, independently of APCs when confronted with their respective antigen, which has been described to be the case in mice (121–123). However, it is known that specialized $CD141^+CD103^+$ DCs are especially effective at cross-presentation for $CD8^+$ T cells in the skin (124, 125).

Regulatory T cells

Similar to other immune cell populations, T_{regs} can reside in non-lymphoid tissue (NLT) such as the skin. Specific residency transcriptional programs in these organs have been described, mediating T_{reg} adaptability to different tissues in mice (126). In human skin, T_{regs} represent between 5% and 20% of all resident T cells under homeostatic conditions (127, 128), where they are known to interact with LCs and fibroblasts (81, 127). Most circulating T_{regs} found in peripheral blood express skin-homing markers which indicates that these cells are constitutively recruited to the skin over other organs (129). Similar to their effector memory counterparts, T_{regs} from the skin are also able to elicit a memory response and have been shown to persist in the skin and induce tolerance to autoantigens in a mouse model (130). In human skin, the function of skin-resident T_{regs} remains elusive, with few studies investigating their function under homeostatic conditions. Other than the canonical transcription factor FoxP3, skin T_{regs} express CLA, as well as the chemokine receptors CCR6, high levels of CCR4, a skin homing marker, high levels of L-selectin and HLA-DR. Similar to their blood counterparts, they express GITR and high levels of intracellular CTLA-4. Contrary to other skin-resident T_{eff} cells, skin T_{regs} tend to express much lower CD103 (127). Seneschal et al. demonstrated that the function of skin-resident T_{regs} is highly dependent upon the context under which they are activated by local LCs. Under steady-state, LCs appear to preferentially activate and expand $CD4^+CD25^+FoxP3^+CD127^- T_{\text{regs}}$, which were functionally competent in suppressing autologous skin resident T_{em} cells. Further, it was suggested that this effect is MHC-restricted, showing that under steady-state conditions, LCs act in concert with T_{regs} to induce and maintain tissue homeostasis (81). While reports of antigen-specific responses by T_{regs} do exist, it is well-established that skin T_{regs} have a high proliferative capacity in response to non-antigen dependent stimuli, such as contact with dermal fibroblasts in combination with IL-15 (127). Other than their immediate immunological function, cutaneous T_{regs} are known to be involved in wound healing (131, 132), where their primary role lies in inhibiting IFN- γ production by other T cells and inflammatory macrophages (132), as well as and modulating hair follicle stem cells (133).

$\gamma\delta$ T cells

In human skin, 1-10% of all resident T cells are estimated to be $\gamma\delta$ T cells (134), with the majority expressing the V δ 1 TCR (135, 136). One known ligand for this TCR is CD1d which is able to present lipid antigens on DCs (137). CCR6 on $\gamma\delta$ T cells is thought to be an important receptor mediating recruitment of activated $\gamma\delta$ T cells *via* CCL20 expression by keratinocytes, DCs as well as endothelial cells (138). CCL20 secretion by keratinocytes is

especially upregulated during acute injury, suggesting an important role for $\gamma\delta$ T cells in response to injury (139). Cytokines important in $\alpha\beta$ T cell maintenance in the skin have also been found to play key roles for $\gamma\delta$ T cell maintenance and development in this organ. IL-7R signaling, for example, has been shown to induce rearrangement and transcription of the TCR γ -chain, and IL-15 is also involved in the expansion of $\gamma\delta$ epidermal T cell precursors as well as their survival, while IL-4 signaling has been shown to promote growth of the epidermal $\gamma\delta$ T cell compartment (140–142). The skin residency marker CD103 has also been implicated to play a role in establishing $\gamma\delta$ T cells in the murine epidermis, with CD103-deficient mice showing significant reduction in $\gamma\delta$ T cell numbers in the skin as well as abrogated morphology in the $\gamma\delta$ T cells present (143). Further, murine CD103 $^-$ DETCs share a competitive niche in the epidermis with CD103 $^+$ T_{rm} , indicating that CD103 is an important determinant in establishing tissue residency in the murine epidermis (113). If CD103 expression by $\gamma\delta$ T cells is also vital in human skin remains to be uncovered. Co-stimulation for $\gamma\delta$ T cells is less understood than for their $\alpha\beta$ counterparts. However, in mice CD27 has been shown to contribute to the function of V γ 2V δ 2 T cell activation and promote IFN- γ production by these cells (144). Further CD2 and ICAM-1 have been suggested as costimulatory molecules for V δ 1 T cells (145–147). Specific functions of $\gamma\delta$ T cells in human skin are known to include regulation of keratinocyte proliferation and homeostasis through the production of insulin-growth factor 1 (IGF-1) and other keratinocyte growth factors (98, 148). Further, $\gamma\delta$ T cells are also able to contribute to skin homeostasis by recognizing damaged cells and exhibit cytotoxic activity *via* the NKG2D receptor (149), as well as perforin secretion and Fas-mediated cell lysis (150).

DC-T cell composition in infection and inflammation

Chronic inflammatory diseases

A skewed composition in terms of T cell numbers and function of skin-resident T cells has been described in a plethora of chronic inflammatory skin diseases. Accordingly, the populations of APCs in inflamed skin also shift, with the dominant subsets being FcER1 $^+$ CD1a lo (inflammatory dendritic epidermal) DCs, CD1c $^+$ CD14 $^{+/-}$ DC (inflammatory), TNF- α $^+$ iNOS $^+$ CD14 $^-$ CD11c $^+$ CD1c $^-$ (TNF- α and iNOS producing) DCs, and CD123 $^+$ pDCs depending on the nature of the disease (88). Further, in a mouse model of skin inflammation, Chow et al. demonstrated that specifically usually resting T_{regs} become highly motile during both adaptive and innate inflammation, highlighting the importance of these cells to control local inflammation (151).

One prominent example of such a disease is psoriasis, which affects 2–3% of the population (152). Skin lesions in psoriasis are thought to be caused by dysregulated cross-talk between APCs and T cells, which leads to an increased production of pro-inflammatory cytokines such as IL-17, IL-12, IFN- γ , TNF- α , and IL-23 (153, 154). This creates a positive feedback loop by recruiting more lymphocytes, neutrophils and myeloid cells to the lesion ultimately causing chronic cutaneous inflammation and epidermal hyperplasia (155). Blocking of TNF- α significantly reduced expression of the DC migration marker CCR7 and its ligand CCL19, thereby supporting clinical remission of patients (156). Dermal CD3⁺ T cells in these skin lesions are often increased by up to 15%. The composition of $\alpha\beta$ and $\gamma\delta$ T cells in psoriasis also shifts, with some studies observing more than 40% of CD3⁺ T cells also expressing $\gamma\delta$ TCRs and secreting the pathogenic cytokines IL-17 and IL-23 (157). Other studies have observed CLA⁺ V γ 2V δ 2 T cells homing to the skin to be increased in patients with psoriasis (158). Further, LCs have been described to preferentially utilize the MAPK-p38 α signaling pathway, which has been linked to psoriasis susceptibility in humans (159). This has been shown to specifically promote production of IL-17 in CD4⁺ T cells by promoting the expression of IL-23 and IL-6, both of which are essential for T_H17 differentiation and known to drive psoriasis pathogenesis (160). Additionally, LCs are able to induce a peripheral T cell response by priming immature CD4⁺ T cells in the lymph node to produce IL-22 which then acts on epithelial cells, further promoting tissue inflammation *via* alarmins such as the antimicrobial peptide HBD3 (161).

While many chronic inflammatory diseases are of unknown etiology, some have been correlated to dysbiosis of the skin microbiota. An example of this is atopic dermatitis (AD), a chronic T_H2-dominated disease characterized by eczematous lesion and severe pruritus caused by immune cell infiltration of inflammatory DCs, macrophages and eosinophils (162). Further, AD is often found to be associated with transepidermal water loss due to a mutation in the filaggrin gene which leads to enhanced susceptibility to overgrowth of pathogenic *S. aureus* (163, 164). Further, patients with acute flares of the disease have been found to have an acute expansion of the cutaneous *S. aureus* population and significant loss of diversity in the cutaneous microbiome. Conversely, resolution of lesions has been associated with a more diverse microbiome composition and contraction of the *S. aureus* population (165). Chronic inflammatory skin disorders still represent a major subset of disease with little mechanistic understanding of how T cell responses are shifted to cause disease.

Infection

It is becoming clear that the capacity of LCs in activating T cells in human skin is highly context dependent with their homeostatic role being more regulatory rather than activating

T_{eff} cells. However, it has been demonstrated that LCs are indeed able to activate skin-resident T_{em} in the context of *C. albicans* infection, driving them to produce effector cytokines such as IFN- γ and IL-17 (81).

As the skin is constantly exposed to pathogens, the pool of T_{rm} in this and other organs is thought to reflect previous infections and exposures. In humans, many CD69⁺ T_{rm} have been shown to recognize prevalent viruses such as influenza A (166, 167), and respiratory syncytial virus (RSV) (168) in the lung. Further, viruses that cause latent and re-activating infections such as herpesvirus (HSV)-1 and -2 (72, 169, 170), Epstein-Barr virus (171–173), and cytomegalovirus (174) are also known to elicit a strong T_{rm} response. This is further corroborated by the correlation between presence of virus-specific T_{rm} and increased immune protection and ability to control infections, which was shown to be the case for RSV (168), hepatitis B virus (175), and HSV-2 (170) infection. Specifically, in HSV infections, CD8⁺ T_{rm} seem to play a crucial role in resolution and protection. HSV-specific CD8⁺ T_{rm} have been found at the dermal-epidermal junction, close to sensory nerve endings which connect the latently infected ganglia to the skin as well as the genital mucosa (72, 170, 176). These cells have been shown to rapidly produce perforin and pro-inflammatory cytokines upon asymptomatic HSV-2 shedding. Further, cluster formation around virally infected epithelial cells and recruitment of CD8⁺ T cells from the dermis (170) emphasize that CD8⁺ T_{rm} are at the forefront of the immune response against acute and latent HSV. While it is now possible to also study T_{rm} in humans, it is worth mentioning that the great majority of current knowledge of T_{rm} behaviour during infection was acquired using murine models of HSV infection which greatly contributed to our understanding of these cells in mucosal tissues (11, 123, 177–180).

Intestine

Similar to the skin, the intestine is constantly exposed to exogenous triggers such as food or microbiota-derived antigens. These antigens are prevented from triggering a pathogenic immune response by cellular barriers. Physically, the intestine is protected by a layer of mucus and glycocalyx which coats the epithelial layer (181) and contains high concentration of secreted IgA (182, 183). In the small intestine, this is composed of a single unattached layer, while the large intestine has two layers of protective mucus, respectively relating to the bacterial burden in each location (184). The intestine is also home to intraepithelial lymphocytes (IELs), other immune cells resident in the lamina propria (LP) and gut-associated lymphoid tissue (GALT), comprising Payer's patches (PP), cecal patches, and colonic patches distributed along the small and large intestine (185). There are differences in immune cell composition between the

small and large intestine which have been extensively reviewed elsewhere (186, 187). A simplified overview of the architecture of the small and large intestine including resident T cells and APCs is shown in Figure 4.

At the bottom of the intestinal crypts, Paneth cells are the main producers of antimicrobial products such as defensins (188) and lysozyme (189), which are secreted into the mucus at the opening of the crypt. Goblet cells, responsible for the production of intestinal mucus, have the ability to take up antigen from the intestinal lumen and deliver these antigens to DCs in the LP *via* a process called goblet cell-associated antigen passage (GAP) (190). Antigens delivered *via* this process have been shown to be taken up by CD103⁺CD11c⁺ DCs which preferentially present to T_{regs}, suggesting that this way of antigen delivery significantly contributes to induction of oral tolerance (191). While this mechanism is not well-understood yet, the more accepted route of antigen delivery from the lumen to the epithelium is *via* M cells on lymphoid follicles (e.g. on Payer's Patches), which can transport whole bacteria (192, 193) that can then be taken up by DCs in the epithelium. This continued sampling of the microbiota by the immune system is crucial to maintaining homeostasis and resistance to pathogens. For example, expression of the chemokine receptor CX3CR1 in mice is essential for APCs to extend their dendrites between epithelial cells and take up intestinal bacteria from the lumen (194) which are then transported to the mesenteric LNs, where production of secretory IgA by plasma cells is induced (195–197). While originally being described as DCs due to their functional properties (194), CX3CR1⁺ APCs were classified as macrophages by others as they also express the macrophage markers CD64 and F4/80 and derive from monocytes (198, 199). Specifically, DCs in the intestine have the major responsibility in establishing tolerance to oral and microbiota-derived antigens. The gut-draining LNs as well as the GALT are the primary sites of T cell priming by intestinal DCs. As in other tissues, many DC

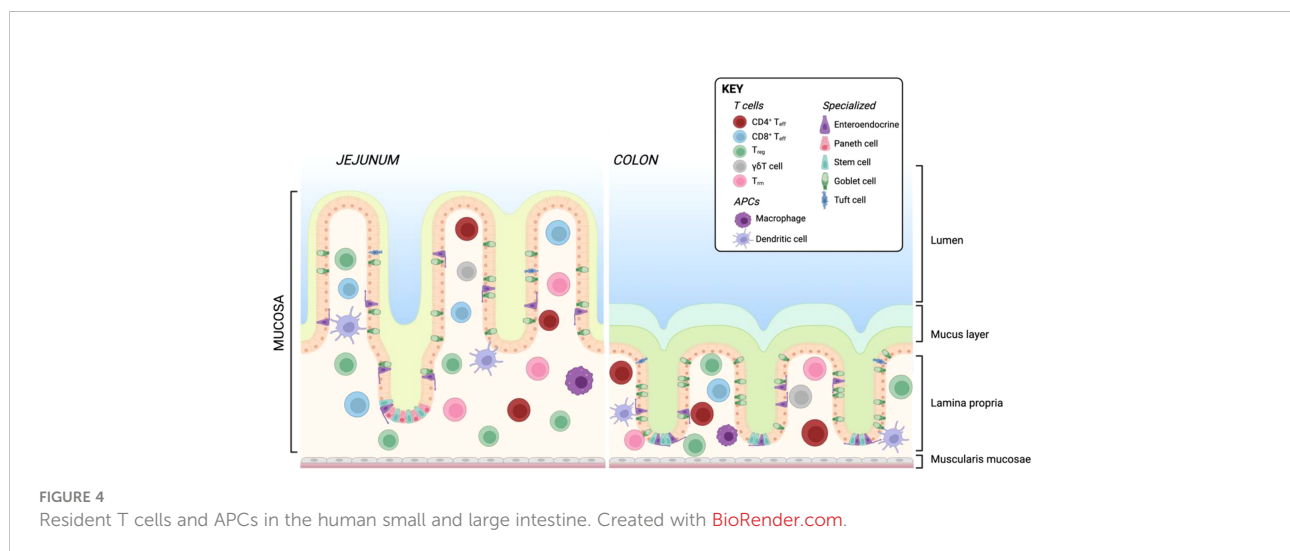
subsets have been identified in the human intestine, with specific subsets more prevalent at specific anatomic locations. In humans, intestinal cDCs are divided into subgroups based on the expression of CD103 and SIRPα (200, 201), with CD103⁻SIRPα⁺cDC2 further subcategorized based on the expression of the chemokine receptor CCR2 (202).

Intestinal cDCs are the only DCs expressing the enzyme RALDH2, which is required for metabolizing Vitamin A to all-trans retinoic acid (RA) (203). This metabolite is required for imprinting gut-homing receptors on T cells, namely α4β7 and CCR9 (204–207). Both CD103⁺ and CD103⁻cDCs in humans have been found to express RALDH2 (208), which is reinforced by expression of RA by stromal cells in the mesenteric LNs (209, 210). In humans, the majority of IELs are T cells, with the highest proportion of non-T immune cells in the colon (211). The highest number of IELs are found in the proximal small intestine, decreasing in the distal small intestine, and lowest numbers in the colon (212). In the adult jejunum, the majority of IELs are CD8⁺αβT cells with a tissue-resident T_{em} phenotype [reviewed in (213)], while the ileum and colon have higher numbers of CD4⁺αβT cells, with a minor population of γδT cells (212). In the LP, CD4⁺T cells dominate over CD8⁺T cells, with the majority of cells exhibiting T_{reg}-like or T_{em} phenotypes (214–217). IL-17 producing CD4⁺T cells are most common in the LP of the colon and ileum, with lowest numbers in the jejunum (216), which is inverse to the distribution of T_{reg}:non-T_{reg} T cells observed in mice (215, 217).

DC-T cell composition in homeostasis

Memory T cells

In contrast to skin, sustained CD69 expression is not necessary for T_{rm} formation in the small intestine (7). Further, in the human intestine CD103 is also not necessary for T_{rm}



persistence (218, 219), and is higher expressed on CD8⁺ T_{rm} than CD4⁺ T_{rm} (216, 220, 221). Human intestinal T_{rm} specifically express CD161, a C-type lectin-like receptor (222, 223), and they share the classic T_{rm} phenotype of downregulating LN homing receptors CD62L and CCR7 as well as the upregulation of adhesion molecules CRTAM and chemokine receptors CXCR6 and low expression of CX3CR1 (224). In the human small intestine, both CD4⁺ and CD8⁺ T_{rm} have been described to survive years, with CD4⁺ T_{rm} exhibiting a T_{h1} phenotype upon reactivation (218, 225). In the gut, it has yet to be elucidated if T_{rm} are continuously replenished from circulating T_{cm} under homeostatic conditions or whether the local population proliferates *in situ*, which has so far not been described. The TCR repertoire of CD8⁺ CD103⁺ vs. CD103⁻ T_{rm} has been described to have low clonal overlap, however overlap between CD103⁻ CD8⁺ T_{rm} was shown to be similar to that of T cells from the peripheral blood, indicating that CD103⁻ T_{rm} are recruited from the periphery and represent an intermediate state between circulatory and resident T cells (218). A study utilizing two-photon laser scanning microscopy revealed that intestinal T_{rm} have restricted mobility (226), indicating that intestinal T_{rm} are able to remain at the site of primary infection.

In mice, memory precursor cells expressing low levels of KLRG1 have been identified as a T_{rm} precursor, whose development is accelerated by DC-derived TGF- β (227). Inflammatory monocytes expressing IL-12 and TNF- β have been shown to suppress TGF- β -induced CD103 expression, leading to an increased population of CD103⁻ LP T_{rm} (228). Additionally, intraepithelial CD103⁻ T_{rm} appear to preferentially develop from KLRG1⁺ T cells over T cells that never express KLRG1 (229). Lastly, while IL-15 is critical for T_{cm} and T_{em} maintenance, this cytokine is not necessary for T_{rm} retention in the intestine (230).

Overall, T_{rm} biology and contribution of antigen presenting cells to T_{rm} generation and maintenance in the human intestine still have many open questions. More detailed reviews on intestinal T_{rm} can be found elsewhere (231, 232).

Effector T cells

While at steady-state, DCs in the gut preferentially induce T_{regs}, with T_{eff} cells being primarily induced during infection or inflammation, which has mostly been studied in mice. Intestinal cDCs “escaping” regulatory conditioning in the gut at homeostasis have, however, been shown to induce tonic protective T_{eff} responses. This escape has been proposed to be mediated by early exposure to TLR ligands and pro-inflammatory cytokines, reducing residency time of cDCs and pDCs in the epithelium and thereby limiting exposure to regulatory-inducing factors (233, 234). Another example of this is p38-MAPK signaling in mouse CD103⁺ DCs, which has been shown to regulate fate-decision between T_{reg} and T_{h1} cells from infiltrating naïve T cells by influencing RALDH2 expression required for T_{reg} induction (235). Further, specific

TLR5 signaling activating CD103⁺CD11b⁺ cDCs induces IL-6 and IL-23 production which promotes T_{h17} development and antimicrobial peptide production (200, 236).

The local microbiota is also essential in inducing T cell subset differentiation and polarization in the gut. In mice, it has been shown that monocolonization with segmented filamentous bacteria (SFB), which are members of the order Clostridiales, can induce the development of LP-resident CD4⁺ T_{h17} cells (237). This selective T_{h17} induction is MHC class II-dependent and requires presentation of SFB antigens by resident intestinal CD11c⁺ DCs (238). The relationship between SFB and T_{h17} has further been demonstrated in mice engineered to express the human antimicrobial peptide HBD5. These mice exhibited loss of SFB which subsequently correlated to a lower percentage of T_{h17} cells in the lamina propria (239).

Regulatory T cells

T_{regs} are central components of establishing tolerance in the intestine and crucial for maintaining homeostasis. Specifically in the gut, T_{regs} are necessary for controlling pro-inflammatory responses to commensal pathogens as well as establish tolerance to food antigens (240–242). Both thymus-derived (t)T_{regs} and periphery-induced (p)T_{regs} have been described in the gut, with pT_{regs} being thought to play the main role in establishing oral tolerance (243, 244), having been shown to control dysregulated T_{h1} responses to food antigens (245). In the colon, the predominant subset of pT_{regs} expresses the T_{h17} master transcription factor ROR- γ t, the expression of which is dependent on the microbiota (245–248). The ROR- γ t⁻ pT_{regs} conversely are critical for homeostasis maintenance in the small intestine (245). In mice, Helios⁺ tT_{regs} in the gut express GATA3 and exhibit a tissue-repair phenotype (246, 249, 250). This GATA3⁺ T_{reg} subset has not, however, been described in humans so far.

TGF- β is an essential cytokine for pT_{reg} differentiation and is, unsurprisingly, present at high concentrations in the intestine (251). DC-derived TGF- β in the gut is essential for local T_{reg} differentiation, which has been demonstrated in mice by ablating expression of the integrin responsible for activation of latent TGF- β (α _v β ₈) on DCs which lead to impaired induction of T_{regs} in the mesenteric LNs (252). Contrarily, deletion of the TGF- β R1 on T_{regs} resulted in normal T_{reg} numbers in the gut (253). However, the authors did not analyze T_{reg} subsets in this study, therefore it cannot be excluded that compensatory T_{reg} expansion was the underlying cause for this observation. Other than cytokines, the metabolite RA is an important contributor to T_{reg} differentiation in the gut. Together with TGF- β , RA has been shown to induce pT_{reg} characterized by upregulation of CCR9 and α ₄ β ₇ (254–256). Particularly CD103⁺ DCs are crucial for this induction, as they show a high expression of RALDH2, the enzyme metabolizing vitamin A to RA (257, 258). Particularly development of ROR- γ t⁺ pT_{regs} is dependent on DC-derived RA (247, 259), further emphasizing that local T_{reg}

induction is crucial to intestinal homeostasis. Other than RA, DCs play a role in T_{reg} induction *via* TLR signaling in the gut. For example, TLR2-mediated recognition of polysaccharide A on the commensal *Bacteroides fragilis* has been shown to trigger induction of T_{regs} and their production of the anti-inflammatory cytokine IL-10 (260).

$\gamma\delta$ T cells

Intestinal intraepithelial $\gamma\delta$ T cells play an extensive role in tissue surveillance, having a high migratory capacity and moving through the intestinal epithelium using occludin-mediated cell-cell contact (261). The majority of $\gamma\delta$ T cells in the human intestine express V δ TCR (262) and have been associated with intestinal homeostasis *via* the production of keratinocyte growth factor 1 (KGF1) (263). Their significant contribution to gut homeostasis has been shown in $\gamma\delta$ T cell deficient mice, showing that mice lacking these cells have reduced intestinal epithelial cell turnover (264), increased susceptibility to dextran sulfate sodium (DSS)-induced colitis (263), and increased gut permeability (265). In humans, intestinal $\gamma\delta$ T expressing NKG2A have been shown to express TGF- β 1, thereby dampening IFN- γ and granzyme B production by co-cultured $\alpha\beta$ T cells from patients with coeliac disease (266). Together, studies so far indicate that intestinal $\gamma\delta$ T cells have an important role in regulating tissue homeostasis and contribute to controlling inflammatory responses in the gut. However, a lot of open questions about their effector functions and interplay with other cells, such as APCs, in humans still remain.

DC-T cell composition in inflammation and infection

Chronic inflammatory diseases

Inflammatory bowel disease (IBD) is a well-known and well-studied chronic inflammatory condition in the intestine and covers ulcerative colitis and Crohn's disease. IBDs have been linked with multiple exogenous factors such as environmental factors, microbiota dysbiosis, and genetic background (267, 268), which culminate in an overall inappropriate immune cell activation in the gut. In IBD, DCs are known to contribute to disease pathology *via* TLR2/4-induced production of IL-12, IL-6, and IL-23 (269, 270), which further impacts T cell polarization and drives T_{H17} -mediated disease phenotypes. $CD103^+CD141^+CD1c^+$ cDCs are reduced in inflamed intestinal lesions, showing functional impairments such as decreased RALDH2 activity (271). Further, some findings have indicated that intestinal inflammation, such as seen in Crohn's disease, impairs normal DC trafficking which consequently leads to dysregulated T cell responses in the gut. For example, CCR7 expression on $CD83^+DC-SIGN^+$ intestinal cDCs is lower in patients with Crohn's disease (272). Further, it has been

observed that leptin production in mesenteric fat is increased in early Crohn's disease patients (273), which has been associated with upregulation of CCR7, maturation and migration of cDCs (274). Whether CCR7 expression is timepoint dependent and what effect this has on T cell priming in Crohn's disease remains to be elucidated.

In recent years, the role of T_{rm} in IBD has become apparent. For example, $CD69^+CD103^+$ T_{rm} -like cells in the LP have been described to be increased in patients with ulcerative colitis and Crohn's disease. Further, the authors could show that increased levels of $CD4^+$ T_{rm} are associated with early IBD relapse (275). Along the same line, Bishu et al. described these $CD4^+$ T_{rm} as functionally competent TNF- α producers in inflamed tissue of patients with Crohn's disease (276). $CD8^+$ T_{rm} have also been implicated in IBD pathogenesis. Bottois et al. described two distinct subsets of $CD8^+$ T_{rm} expressing KLRG1 and CD103, showing that $CD103^+$ $CD8^+$ T_{rm} in Crohn's disease patients exhibit a T_{H17} -like phenotype, while highly proliferative $KLRG1^+$ $CD8^+$ T_{rm} present with increased cytotoxic effector function and are overrepresented during acute inflammation (277). Single-cell RNA-sequencing studies of ulcerative colitis also showed transcriptional changes in the $CD8^+$ T_{rm} compartment, with an increased inflammatory signature (278, 279). In a recent publication using mass spectrometry, HLA-DR $^+$ CD38 $^+$ $CD4^+$ T_{em} were found to be enriched in lesions of Crohn's disease patients. The authors could further use imaging mass cytometry of tissue sections to show co-localization of memory $CD4^+$ T cells together with HLA-DR $^+$ CD11c $^+$ DCs located below the epithelial layer in the inflamed regions of the intestine (280). T_{rm} with a regulatory signature have also been described to be reduced in IBD, characterized by $CD103^+Runx3^+$ and expression of the regulatory-associated molecules CD39 and CD73 together with IL-10 production (281). Furthermore, studies revealed a decrease in both the $CD103^+$ $CD8^+$ and $CD4^+$ T_{rm} compartment during active IBD, which recovered during remission phases, whereas the opposite observation was made for $CD103^-$ T_{rm} (282). These studies further demonstrate the heterogeneity of intestinal T_{rm} and are likely a reflection of T_{rm} plasticity during different phases of the inflammatory response.

Infection

While the physical barriers like the intestinal mucus protect against food-borne pathogens and harmful commensals (known as pathobionts), many microbial organisms have evolved to evade host defense and cause infections. Infections with such enteric pathogens are most commonly associated with diarrhea, which is a major cause of death worldwide (283). The most frequent enteric infections are with *Salmonella* spp. and *Campylobacter* spp (284), with other examples being *Vibrio cholerae*, *Shigella* spp. and certain strains of *Escherichia coli* (285). The most common pathobiont infections are caused by *Enterococcus* spp (286), and *Clostridium difficile* (287).

While TLR2 is important in inducing T_{regs} (see above), TLR5, the receptor for bacterial flagellin (288), has been implicated in the host response to invasive pathogens such as *Salmonella* spp. CD11c⁺ LP-resident DCs express TLR5, which is important in modulating DC movement, as TLR5-deficient mice have increased survival and lower dissemination when infected orally with *Salmonella* spp. whereas no difference was observed when mice were infected intraperitoneally (289). This observation indicates that trafficking to the mesenteric LN by DCs is impaired thereby preventing dissemination of the infection. Another important consequence of TLR-mediated activation of DCs is cytokine production. A crucial cytokine in the gut produced by DCs in response to infection is IL-23, which has been linked to infection with pathogens like *Salmonella* spp (290), *C. rodentium* (291), and *C. jejuni* (292). The receptor for IL-23 in the gut is expressed on multiple immune cells such as $T_{\text{h}}17$, NKT, $\gamma\delta$ T cells and ILCs (293, 294). IL-23 receptor signaling in turn triggers production of IL-17 and IL-22. IL-17 appears to have time-dependent effects during intestinal infection. During early *Salmonella* spp. infection, IL-17 produced in the caecum is primarily mediated by $T_{\text{h}}17$ cells and to a lesser extent $\gamma\delta$ T and NKT cells (295, 296). Another example of the importance of $T_{\text{h}}17$ -mediated immunity during infection has been shown in rhesus macaques where SIV-induced depletion of $T_{\text{h}}17$ cells leads to erosion of the mucosal barrier and increased dissemination of *S. enterica* Typhimurium to the mesenteric LNs (296). IL-17A or IL-17F deficiency in mice lead to increased pathology in response to *C. rodentium* infection (297).

The IL-23- $T_{\text{h}}17$ axis is also important in human intestinal infection. Patients suffering from *C. jejuni* infection show increased percentages of $T_{\text{h}}1$ and $T_{\text{h}}17$ cells, as well as increased levels of the respective effector cytokines. The authors could show that when intestinal epithelial cells were treated with IL-17A or IL-17F, intracellular survival of *C. jejuni* was significantly decreased, emphasizing the importance of these cytokines in human infection (292). Further, IL-17 expression was also detected in the duodenum of patients recovering from *V. cholerae* infection, the causative agent of cholera. Kuchta et al. observed that in patients suffering from acute cholera, IL-17 expression was increased compared to later disease stages or healthy subjects, suggesting that *V. cholerae* infection also induces an immediate mucosal $T_{\text{h}}17$ response (298).

The other IL-23-induced cytokine important in intestinal infection is IL-22. In general, IL-22 is associated with tissue repair and is known to be a major inducer of antimicrobial peptide production by mucosal epithelial cells (299, 300). In the context of infection, IL-22 has been found to increase colonization resistance to the pathobiont vancomycin-resistant enterococci (236). Similar to IL-17, IL-22 has also been shown to have time-dependent effects. During early infections, IL-22 is primarily produced by ILCs and only later on by T cells. This was demonstrated by Ahlfors et al, showing that during infection

with *C. rodentium* IL-22 is initially produced by ILC3s and then by CD4⁺ T cells (301).

Overall, it has become clear that the DC-induced IL-23- $T_{\text{h}}17$ axis is particularly important in response to intestinal infection by modulating epithelial microbial peptide expression and preventing dissemination of intestinal infection.

Female reproductive tract

The immune system in the FRT has a dual role as it protects the barrier tissue against pathogens transmitted during sexual intercourse, and promotes tolerance to foreign antigens necessary to allow fertilization and embryo development. As these two diametrical roles are important at specific times during the menstrual cycle, the composition of immune cells undergoes major fluctuations. During menstruation, a much higher density of CD1a⁺ DCs was observed in the human uterus compared to proliferative and secretory phase (302). Uterine macrophages increase constantly in numbers during secretory phase and peak at menstruation, while the total number of T cells remains constant (303–305). The sex hormone progesterone does not only inhibit activation of DCs (306), but also causes polarization of T cells into $T_{\text{h}}2$ and T_{reg} direction (307, 308). Moreover, subsets of immune cells do not only change during the menstrual cycle, but also differ when comparing tissues from pre- and postmenopausal females (309). There are substantial differences between the structure and physiology of the female genital tract between the most frequently used animal model of mice compared to humans, as the murine uterus contains two uterine horns and also the estrous cycle has a length of around 5 days compared to 28 days in humans. However, due to the previously low interest in female reproductive health, scientists started only recently to investigate immune cell populations in large scale in the FRT of humans. Therefore, most knowledge on the female genital immune system was obtained in mice (310). With this section, we aim to shed light on specific features of antigen uptake and presentation as well as T cell responses in the female genital tract and raise awareness for inflammatory conditions and chronic infections.

The female genital tract is structured in several parts: the lower reproductive tract lined with multilayered stratified epithelia forming vagina and ectocervix, the endocervix as an interphase and the upper genital tract with single columnar epithelium forming the uterus, adjacent to the fallopian tubes stretch connecting the ovaries with the uterus which are composed of secretory and ciliated columnar epithelial cells (Figure 5). The main APC subsets in the human vaginal tissue are, similar to skin, in the epithelial layer LCs characterized by CD207 expression and in the lamina propria DCs characterized by expression of CD1c as well as CD14 on a specific subset (311, 312). In addition to DCs, another frequent APC subsets in the vagina are CD1c⁻CD14⁺ macrophages additionally having

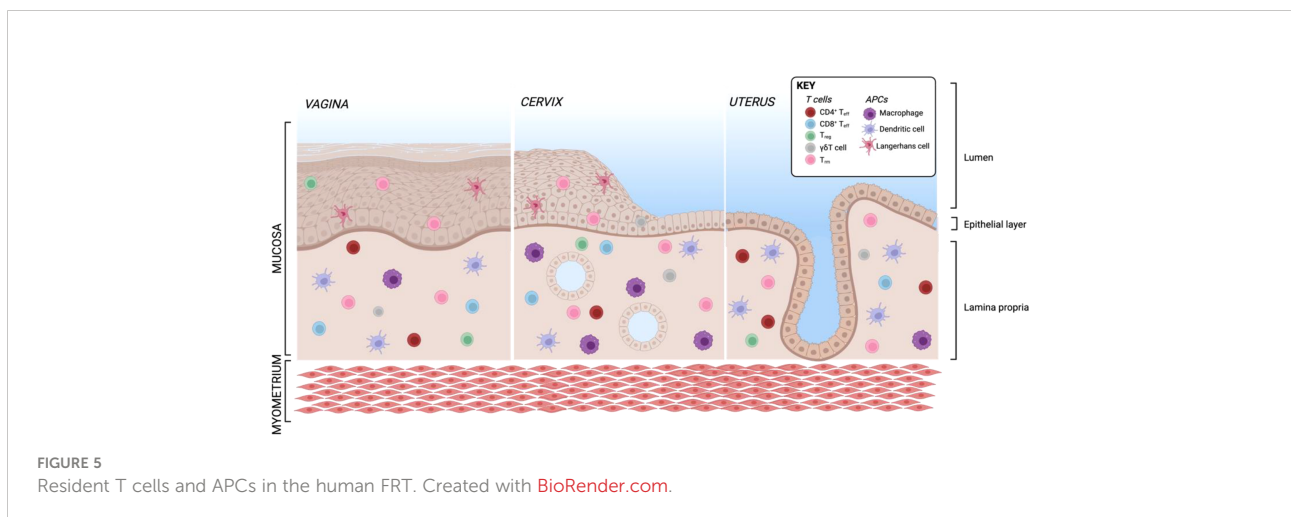
CD163 on their surface (311, 312). In the cervix, the most frequent immune cell population are macrophages which make up more than 25% of all CD45⁺ immune cells (55). CD11c⁺CD14⁺ DCs accounting for another approx. 20% of immune cells are the most common DC subset and a large proportion also express DC-SIGN. Other DC subsets such as CD11c⁺CD14⁻ myeloid DCs and CD123⁺ plasmacytoid DCs were described in low numbers (55). The percentage of APC subsets within CD45⁺ immune cells is quite similar in cervix and uterus, however, the APC compartment in the uterine endometrium shows some substantial differences. There are less DC-SIGN⁺ DCs and DCs expressing CD103⁺ involved in antigen sampling and migration were almost exclusively found in the endometrium (313). In the murine endometrium, both CD103⁺ and CD103⁻ DCs migrate to the local lymph nodes upon antigen challenge. The CD103⁺ DCs preferentially present antigens to T_{regs}, whereas their CD103⁻ counterparts were shown to stimulate an effective CD4 T cells response (314). In the murine uterus, DC in the decidual of pregnant females were shown to be trapped in the tissue, despite keeping responsiveness to pro-inflammatory stimuli and migration capacity towards CCL21 (315). This indicates that by preventing DC trafficking to the draining LN, T cell tolerance to fetal antigens is promoted. Single-cell sequencing of human uterine samples during secretory and proliferative phase revealed presence of myeloid cells during both phases, being composed of DCs as well as M1- and M2-polarized macrophages (316). CD11c⁺ DCs can be further divided into CD11b⁺⁺ and CD11b^{lo} DCs, with the CD11b⁺ expressing DCs being the most abundant subset in all tissues of the FRT and correlating with CD14 expression (313). In the vagina, the ratio of CD4 to CD8 cells is almost equal, with an increasing ratio towards endocervix and ectocervix (55, 317). In the uterus, however, CD8 T cells represent the predominant

subset (55). B and NK cells make up less than 5% of immune cells in the human ectocervix and are not in focus of this review (55).

DC-T cell composition in homeostasis

Memory T cells

In general, most T cells in the female reproductive tract are T_{rm} being CCR7⁻CD45RA⁻. More than 80% of cervical T cells express CD69 within both stroma and epithelium (317, 318). The marker CD103 being associated with a T_{rm} phenotype in other tissues is in the cervix almost exclusively present on epithelial CD8 T_{rm} (318), but also enriched on vaginal CD4 T_{rm} (317). These vaginal CD103⁺CD69⁺ CD4 T_{rm} show a T_h17 signature including high expression of RORC, IL-17A, IL-17F and IL-22 (317). A recent publication used T_{rm} derived from human cervix to assess antigen-specific CD4 and CD8 response against HSV-2 (319). An elegant mouse study using parabiosis models revealed that CD8⁺ T_{rm} in the mucosa undergo proliferation *in situ* after mucosal rechallenge independently of CD11c⁺ DCs (114). On the other hand, bystander memory CD8 T cells consisting of T_{cm} and T_{em} are recruited during local challenge without antigen recognition and develop a T_{rm}-like phenotype by upregulating CD69, but not CD103 (114). To investigate how the recruitment of bystander memory cells to sites of infection as well as tissue autonomous amplification of local T_{rm} contributes to immunity in the human FRT, it is important to apply functional models with human cells and validate other experimental approaches in the future. To date, the T_{rm} subset is the best studied immune cell subset in the FRT and will be discussed further in the sections about the respective infectious diseases.



Regulatory T cells

Recently, T_{regs} were shown to make up around 15% of the CD4 population with comparable percentage within all tissues from the lower FRT, including vagina, endocervix and ectocervix (317, 320). It is reported that T_{regs} are induced in the decidua of mice and humans to protect the developing embryo from the immune system of the mother, nicely summarized in the following reviews (321–323). However, T_{regs} can also have an unfavorable role if they dampen the immune response against sexually transmitted infections such as human immunodeficiency virus (HIV), human papilloma virus (HPV) or chlamydia. In a mouse model of intravaginal *N. gonorrhoea* infection $\text{TGF-}\beta^+$ T_{regs} were induced in cervix-draining lymph nodes, thus evading the immune response and enabling pathogen survival (324). The occurrence of T_{regs} in the mucosal tissue is described for several pathogens and conditions, while the mechanisms of their induction still need to be elucidated.

$\gamma\delta$ T cells

Human studies revealed a $\gamma\delta$ T cell percentage ranging from 5% to 10% of $\text{CD}3^+$ T cells depending on tissue sampling during the proliferative phase or secretory phase. The majority of them expressing V δ 1 (325, 326), but CCR5 can be found on the surface of both V δ 1 and V δ 2 (327). HIV infection significantly reduces the number of $\gamma\delta$ T cells in the cervix (327). Abnormal vaginal flora due to bacterial vaginosis was shown to change the composition of vaginal $\gamma\delta$ T cells to higher levels of V δ 2 (328). Beside their role during infection, $\gamma\delta$ T cells seem to be involved in tolerance induction during pregnancy. The decidua of women with spontaneous abortions showed increased numbers of $\gamma\delta$ T cells with an additional upregulation of V δ 2⁺ cells (325). In the murine female genital tract, $\gamma\delta$ T cells represent a much higher proportion of immune cells and express preferentially IL-17A under steady state (329). As IL-17A was described to be essential for resistance against fungal infection, a murine study revealed that TCR $\gamma\delta$ deficient mice are more susceptible to *C. albicans* growth in the FRT (330). To date, our knowledge about $\gamma\delta$ T cells in the FRT is still limited and remains to be addressed in different disease settings.

DC-T cell composition in infection

Viral infections

CD4 and the chemokine receptors CCR5 and CXCR4 are hijacked by HIV. Beside T cells, this repertoire of receptors is found on all four APC subsets in the vagina in different quantities, indicating a role of these cells during HIV acquisition and transmission to other cell types (311). It was shown that exclusively $\text{CD}14^+$ DCs take up HIV virus-like particles and express CCR5 ligands (313). The type-I interferon inducible lectin Siglec-1 expressed on $\text{CD}14^+$ DCs

was identified to play an indispensable role in HIV uptake and transmission to CD4 T cells which can be blocked by anti-Siglec-1 antibodies (331). As $\text{CD}14^+$ DCs are most frequently occurring in the ectocervix, this tissue is highly relevant to study HIV transmission (313, 332). $\text{CD}4 T_{\text{rm}}$ from the ectocervical region expressing CD69 are characterized by high CCR5, thereby function as a primary target for HIV infection and persistence (333, 334). Numbers of $\text{CD}4 T_{\text{rm}}$ are significantly decreased in cervix tissue of infected individuals, but increased activation can be observed (333). In the same lines, $\text{CXCR}3^+$ T_{rm} in the skin and anal mucosa of HIV infected individuals starting antiretroviral therapy late remain constantly depleted, thereby creating an optimal environment for HPV related cancer development (335). HIV-infected individuals show increased T_{regs} and reduced $T_{\text{h}}17$ cells, the ratio between these two cell types can be restored by anti-retroviral therapy (ART) (336). The percentage of T_{regs} remained increased even under ART and was associated with a skewed ratio of CCL17/CCL20 in the ectocervix samples of these women (336), indicating that APCs as major source of those cytokines, are causing the disbalance of T cells in these conditions.

Infections with HPV are widespread and almost every human encounters HPV during their life time. There are several different types, with only some of them being transmitted sexually and causing infections that can lead to cancer development in the cervix. Patients with HIV infection possess an increased risk to develop HPV associated cancer with T cells as important players in the course of HPV-related malignancies (337, 338). Upon HPV infection, T cells in the cervix obtain a more activated profile by upregulation of HLA-DR, independent of HIV status of the patients (339). However, in patients with a co-infection of HIV and HPV, lower numbers of CD4 T cells were observed compared to HPV-negative HIV-infected patients (339). In individuals with HPV-associated genital warts, an accumulation of T_{regs} was reported (340). It was shown that T_{regs} are attracted by CCL17 and CCL22, which are mainly produced by $\text{CD}1a^+$ LCs and macrophages within the warts, respectively (340). Trafficking of APCs such as LCs is impaired in HPV lesions, as the chemoattractant for (CCL20) and activation pattern of LCs (CCR7, CD80 and CD86) seem to be decreased (341–343). Also, $T_{\text{h}}17$ cells seem to play a role in progression of HPV-related intraepithelial cervical neoplasia (CIN), as patients with high CIN or cervical cancer exhibit high numbers of $T_{\text{h}}17$ cell in the blood, which is correlated with high IL-17 levels in the cervix tissue (344). In a study assessing the T cell infiltration in cervical cancer patients, $\text{CD}103^+$ CD8 T cells infiltrate the tumors and are associated with good prognosis (345). These findings indicate that a $T_{\text{h}}17$ and T_{reg} response is correlated with progressive HPV infection, whereas CD8 T cells are beneficial. However, most studies focus on late stages in CIN progression/tumor development and little is known about early processes of HPV infection.

Bacterial infections

Infections with chlamydia are the most common bacterial sexually transmitted infection in humans. However, most of our knowledge of immune reactions during chlamydia infections was obtained in mice, as studying immunity against *chlamydia trachomatis* (Ct) is connected with many difficulties, such as the high number of asymptomatic cases and the development of tolerance instead of immunity when using inactivated bacteria. The later problem was addressed in a mouse model by Stary et al. showing that live and UV-inactivated Ct are taken up by either CD103⁻ and CD103⁺ DC subsets, causing priming of immunogenic effector T cells or T_{regs}, respectively (314). In mice, induction of T_h1 cells plays a huge role in conveying protective immunity, whereas stimulation of CD8⁺ T cells was suggested to play a role in chronic inflammation and cause tissue destruction rather than advancing protective immunity in mice (314, 346, 347). T_h1 polarization initially relies on IL-12 production by DCs, as IL-12 deficient mice had prolonged times of chlamydia shedding (348). In fact, the most important immune mechanism for chlamydia clearance is IFN- γ , as T-bet deficient mice could not control *chlamydia* growth, but T cells shifted to a more T_h17 response, whereas IFN- γ or IFN- γ -receptor deficient mice die from systemic infection (349, 350). T_{rm} of the FRT seemed to be essential to protect against subsequent chlamydia infection (314). However, a recent publication suggests that also circulating memory T cells can protect against infection without being primed in the tissue (351). Apart from conveying protective immunity, T cells can also be involved in undesirable responses causing FRT pathology and chronic inflammation. Especially activation of non-antigen-specific CD4 as well as CD8 bystander cells can exacerbate the pathology in a mouse model of chlamydia infection (352). The presence of T_{regs} was on the one hand shown to exacerbate Ct infection (314), on the other hand, they are described to skew T cell differentiation into a T_h17 direction, which was correlated with increased pathology in a *chlamydia muridarum* mouse model of infection (353). Together, these findings suggest that the T cell response during Ct infection is highly plastic and the induction of a certain cytokine milieu is essential.

Discussion

All the same: Commonalities and differences in tissue APC-T cell crosstalk

When comparing the three different tissues summarized in this review, some overarching themes are apparent: The majority of T cells in tissues are T_{rm} cells (7), closely followed by T_{regs} (19, 20), both cell types reflecting the constant exposure to environmental compounds and antigens in barrier tissues and the need for a balance between immune tolerance and reaction. Further, DC subsets are responsible for controlling this balance,

but they are often described by different markers in different tissues and their subsets appear more tissue-specific than those of T cells, whose identity is often easier to define across tissues. However, some clear differences exist also in T cells. Expression of CD69 and CD103, canonical T_{rm} markers in the skin (13, 111) and FRT (317, 318), seem dispensable for T_{rm} establishment in the intestine (7). T_{rm} are relatively stationary within the respective tissue, however, there are quite substantial differences in motility between T_{rm} in different tissues, as T_{rm} in the FRT move up to 5-times faster compared to T_{rm} in skin epidermis, probably depending on the architecture of the tissue and density of the structural cells (114). While CD4⁺ and CD8⁺ T_{rm} exist in all discussed barrier tissues, the skin harbors more CD8⁺ T_{rm} than the intestine and the FRT, where the distribution of CD4⁺:CD8⁺ T_{rm} is approximately equal (218, 225). Further, T_{reg} induction in the intestine is highly dependent on RA produced by local DCs (254–256) and in the FRT, progesterone (307), independently of DCs, appears to take a similar role, while no hormones or metabolites are yet identified to induce T_{regs} in the skin. In general, it appears, that while all barrier tissues are continuously exposed to microbial antigens, only the intestine has dedicated DC subsets to specifically induce T_{regs} to promote tolerance against the microbiome (191). This observation fits with the fact that, in the skin, most T_{regs} respond and get activated by non-antigenic stimuli while most T_{regs} (127) in the gut are antigen specific (240–242). In general, aside from their function in maintaining immune tolerance, the function of T_{regs} in different tissues is often diverse, ranging from direct suppression of activated immune cells to aiding in tissue repair (19, 20), thereby emphasizing the need to characterize these cells and their non-canonical functions in a tissue context better. Similar to this, $\gamma\delta$ T cells exhibit both regulatory and cytotoxic functions across tissues even though their distribution is tissue-specific (V δ 1 in the skin, V δ 7 in the intestine, V δ 1 and V δ 2 in the FRT) (149).

During an immune challenge in barrier organs, such as during infection, T_{rm} are poised locally in all three tissues, reacting to previously encountered antigenic stimuli directly. Further immune responses are induced by APCs which traffic to the respective draining lymph nodes and recruit T_{eff} cells to the tissue. T_h17 responses are crucial in controlling infections, both bacterial and viral (313, 332). Interestingly, the same responses and effector cytokines are also often the ones that are pathogenic in chronic inflammatory diseases (153, 154). How and why exactly these exacerbated immune responses cannot be controlled by tissue-resident T_{regs}, which are present in barrier tissues in great abundance under homeostatic conditions, has yet to be elucidated. However, all chronic inflammatory diseases discussed in this review are characterized by a decrease in tissue T_{regs}, but whether this is cause or effect of chronic tissue inflammation and what role APCs play in this shift of T cell subsets during chronic inflammation remains a big question that should be the topic of further research.

Into the (un)known: On big data, future perspectives, and individualized therapies

Previous dogmas of dividing immune responses strictly into pro- and anti-inflammatory immune cell subsets are outdated. The more we learn about tissue-specific immune responses, the more we understand that there is not the one beneficial and harmful immune cell subset to every disease. It is more a fine-tuned balance act between APCs and T cells to enable immunity against pathogens but protect the host from autoimmunity. With current advances in single-cell RNA sequencing (scRNA-seq) and multichannel flow cytometry, we will be able to get a better insight, which players are involved in regulating immunity during homeostasis. scRNA-seq has specifically enabled much greater insight into molecular mechanisms of tissue immunity as well as led to the discovery of new immune cell subsets or new definitions of existing subsets. This is especially valuable since this approach allows for the acquisition of a large amount of data from, often limited, human material. Further, a lot of information that is derived from these big data experiments would be impossible to acquire using traditional experimental models as it is now possible to also model *in vivo* dynamics from these datasets, such as the interplay between different cell types (354, 355) and temporal dynamics across the development of organs (356–358), and tracking T cell clones across tissues (359, 360). Analyses like these have revealed novel regulatory T cell-APC interactions at the maternal-fetal interface important for embryo implantation (361), a renewed focus on pDCs in skin inflammation (362), novel V δ 1 T cell effector subsets (363), and detailed profiling of different immune niches and interactions across the human intestine (54). Further, a better understanding of tissue adaptation of different immune cells is becoming appreciated, highlighting basic principles of immune biology in barrier tissues but also appreciating that these cells have the potential to specifically adapt to the local tissue environment and how this changes in disease (126, 364–366). As highlighted in this review, communication between different immune cell types is absolutely essential in determining the outcome of an immune response and understanding this interplay at a deeper level in local tissues is an important step towards developing new therapeutic avenues that can act in a much more targeted manner than previously possible. Further, the plasticity of immune cell subtypes, especially APCs and T cells, is becoming more appreciated as having whole transcriptome data can separate cell types that were previously indistinguishable and is an important step towards understanding fundamental changes during disease development. As this knowledge progresses, it will be interesting to see if we will gain a better understanding of responses to immunotherapy and why some patients benefit while others do not. Moreover, this technical evolution will also allow to come away from animal models and help uncover tissue-specific

differences as well as overarching themes in immune defense in barrier tissues. In addition, we want to emphasize the importance of investigating the interplay of different human immune cell subtypes in complex 3D model systems to further validate findings from big data-based models and how these can be translated to patient care. It will be crucial to define the function of rare DC subsets, T_{regs} or $\gamma\delta$ T cells as they seem to have a major role in immune balance despite their low frequencies. Especially the mechanisms balancing different $\gamma\delta$ T cell subset or T_{regs} and T_h17 cells will be an important focus for further studies. In the future, integrating different large datasets will be highly valuable in better understanding more complex disease systems, such as metabolic dysregulation as well as epigenetic modifications. Together, these data will yield a clearer picture of biological networks and how they are perturbed in different diseases. Currently, we are at the start of a new era of understanding biological mechanisms that lead to disease and disease progression. In the future, insights gained from these basic studies will in turn re-shape how therapeutics are developed and most likely emphasize the importance of more patient-specific approaches to health care.

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Conflict of interest

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