The human cutaneous chemokine system

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INTRODUCTION

Chemokines control leukocyte migration and fulfill essential functions in homeostatic and inflammatory immune processes. Homeostatic chemokines control leukocyte traffic taking place in the absence of inflammatory stimuli whereas inflammatory chemokines are inducible and, therefore, control effector cell recruitment to the site of infection and disease where inflammatory chemokines are being produced. Chemokines and their receptors do not work alone but instead require the concerted “trans” action of cellular adhesion molecules that, figuratively speaking, provide the necessary “traction” for cell migration. The combination of chemokine receptors and adhesion molecules define distinct address codes, based upon which leukocytes can either remain in circulation or become engaged in secondary lymphoid organs or gain access to peripheral tissues. The checkpoints for leukocyte relocation are (i) the microvascular beds where selected leukocytes exit the bloodstream via trans-endothelial migration, (ii) the specific site(s) of chemokine production within the tissue where migrating leukocytes interact with their target cells, and (iii) the lymphatic vasculature controlling leukocyte exit from healthy or inflamed tissues. Detailed knowledge about a cell’s address code provides much information about its functional “quality.” Consequently, the expression studies of distinct chemokine and adhesion receptor combinations have been useful in functionally defining the various leukocyte subsets, as best exemplified by distinct classes of T helper cells. In humans, most chemokine studies have been performed with fresh or cultured leukocytes derived from peripheral blood. Here, we summarize our current knowledge about the chemokine system in human skin and compare it (where allowed) with the situation in mice. Human skin is constantly exposed to a large variety of environmental hazards that include UV irradiation, toxins, as well as commensal, and pathogenic microbes. The species-specific environment and extended life span may explain in part why human skin differs profoundly from standard laboratory animals (rodents) in terms of tissue architecture and immune cell composition. We will discuss the role of chemokines in regulating tissue-selective homing of memory T cells with particular focus on human skin, and propose a model whereby the skin-selective homing of immune surveillance T cells in humans is regulated by CCL1 and its ligand CCR8. We also raise several unresolved issues that are relevant for understanding tissue immune surveillance and vaccination responses.

THE SKIN VERSUS GUT HOMING DICHOTOMY

Several excellent review articles discuss the substantial progress achieved in mouse experiments targeting the role of chemokines and adhesion molecules in the tissue-specific homing of leukocytes (Agace, 2008; Mora et al., 2008; Sigmundsdottir and Butcher, 2008; Woodland and Kohlmeier, 2009; del Rio et al., 2010). This research was based on earlier observations describing the correlation between the sites of immune activation (vaccination) with the instruction of tissue-homing properties in effector/memory
T cells during immune response initiation in the draining lymph nodes. In essence, the current paradigm is simple and calls for the targeted release of tissue-derived factors during T cell priming that instruct the tissue-specific leukocyte homing. For the gut, the expression CCR9 together with α4β7 (or αEβ7) has been correlated with the metabolism of vitamin A (retinol; Figure 1). The bulk of dietary vitamin A is stored in the liver and is released in the form of a complex with a protein chaperon (retinol-binding protein) to ensure a steady-state level in blood circulation and peripheral tissues (Niederreither and Dolle, 2008). The necessity of vitamin A in organ development and eyesight is well established, but it is becoming increasingly clear that vitamin A metabolites also affect DC functions and, as briefly discussed here, T cell mobilization. In the gut, CD103+ DCs process vitamin A to retinoic acid (RA), which acts on the nuclear receptors, composed of the retinoic acid receptor (RAR), and the retinoic X receptor (RXR). Of note, RXR is also shared with the vitamin D receptor (VDR; see below). Elegant studies have now shown (i) that RA instills gut-homing receptors (CCR9, α4β7) on murine T cells (Iwata et al., 2004), and (ii) that gut-associated DCs express elevated levels of vitamin A-processing enzymes leading to the localized release of RA that triggers CCR9 and α4β7 expression in T cells (Coombes et al., 2007; Jaensson et al., 2008; Guilliams et al., 2010). The proximity of DCs and T cells may ensure the undiluted transfer of DC-derived factors, including RA, to responding T cells in the lymph nodes, although the underlying mechanisms have not been studied. Mouse studies have revealed that RA production is a particular feature of CD103+ DCs, which predominate in gut tissue whereas CD103− DCs are less efficient in doing so (Johansson-Lindbom et al., 2005; Jaensson-Gyllenback et al., 2011). Intestinal CD103+ DCs and RA are also involved in the induction of CCR9 and α4β7 in humans T cells (Jaensson et al., 2008; Eksteen et al., 2009). Still, further studies are needed to evaluate the relative contribution of gut DCs versus tissue cells, such as intestinal epithelial cells that are also capable of producing RA (Edele et al., 2008), or lymph node stromal cells, which may be responsible for licensing DCs to process RA (Hammerschmidt et al., 2008; Molenaar et al., 2009). Nevertheless, the selective metabolism of vitamin A by gut-associated CD103+ DCs and its effect on expression of gut-homing receptors on T cells fits nicely with the above-mentioned tissue-homing paradigm.

With respect to skin, recent evidence suggest the involvement of another vitamin, vitamin D₃, and especially its active metabolite 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃), as the environmental cue for induction of the skin-selective homing receptor CCR10 (Mora et al., 2008; Sigmundsdottir and Butcher, 2008; FIGURE 1). Vitamins and vitamin precursors are provided by the diet and, in the case of vitamin D₃, sun exposure and stored as inactive precursors in the liver or bile. Vitamins A and D precursors can be further processed to their active metabolites, retinoic acid (RA), and 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃), respectively, by tissue-resident dendritic cells and, in some cases T cells, by processes involving intracellular hydroxylases (P450) and dehydrogenases (ALDH, RALDH). These active compounds bind to vitamin D (VDR–RXR) and retinoic acid (RAR–RXR) receptors in the nucleus leading to induction of gene expression, which affects both DC maturation and T helper cell differentiation. RA and 1,25(OH)₂D₃ signaling in DC have both been shown to promote IL10 production and skew T cell differentiation toward Th2 and Treg development, while signaling in T cells affects the expression of adhesion molecules and chemokine receptors. Specifically, activation of RAR–RXR-dependent gene expression leads to the expression of the gut-homing receptors CCR9 and α4β7, while activation of VDR–RXR induces CCR10 expression but not the expression of CLA, the skin-specific ligand for E/P-selectin. 1,25(OH)₂D₃, 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃); RA, retinoic acid, P450, cytochrome P450; ALDH, alcohol dehydrogenases; RALDH, retinal dehydrogenases, VDR, vitamin D receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor.
Vitamin D3 is metabolized to its active form, 1,25(OH)2D3, by 2009). In fact, there is no need for dietary vitamin D3 supplementation, except in immunosuppressed patients (e.g., transplant recipients) who need to avoid sun exposure and in the elderly. Vitamin D3 is metabolized to its active form, 1,25(OH)2D3, by hydroxylases in the liver and kidney as well as in skin cells, including keratinocytes and dendritic cells. Similar to RA, 1,25(OH)2D3 binds to heterodimeric nuclear receptors composed of the VDR and RXR, which then trigger gene expression by interacting with vitamin D response elements (VDREs). More importantly, VDREs are present in the promoter region of human but not mouse CCR10, which may explain the inability of 1,25(OH)2D3 to induce CCR10 expression in mouse T cells (Sigmundsdottir et al., 2007). Nocturnal or furry animals, which lack cutaneous vitamin D3 production, likely evolved a different mechanism for imprinting skin homing properties in effector/memory T cells. This is supported by the finding that skin-derived DCs from both mice (lacking vitamin D3 metabolites) and humans are capable of inducing a skin homing phenotype in responding T cells, indicating that certain, as yet undefined skin “factors” are likely to instruct local DCs in both species (Mora et al., 2005). Furthermore, the tissue-homing program of peripheral DCs can be overridden when exposed to alternative tissue environments, demonstrating the plasticity of DCs to instruct tissue-homing properties in T cells and, importantly, the presence of multiple and functionally overlapping tissue factors (Dudda et al., 2005; Rimoldi et al., 2005; Edele et al., 2008; Hammerschmidt et al., 2008; Iliev et al., 2009).

The vitamin A-vitamin D3 dichotomy in controlling homing properties in T cells during peripheral immune responses provides a plausible explanation for the observed traffic of engaged T cells to distinct peripheral sites. But many more questions remain.

VITAMINS

The finding that vitamin A induces CCR9 and integrin receptor expression in T cells represents an important discovery (Iwata et al., 2004). Yet, it is undisputed that the principal role of vitamin A (and vitamin D3) is not the instruction of T cell migration programs but rather the control of crucial and diverse metabolic processes. Vitamin A metabolism also occurs in sites other than the gut, including skin, where the treatment of disorders of keratinization, such as Psoriasis, using topical, and/or oral retinoids is well established (Roos et al., 1998). In addition, vitamin A controls integrin α4 expression, which when combined with the β1 chain is frequently involved in T cell recruitment to inflammatory sites (Kang et al., 2011), and vitamin D3 was shown to inhibit the expression of the skin homing adhesion molecule CLA (Yamanaka et al., 2008). Furthermore, vitamins A and D3 have a general effect of DC function leading to Th2 and iTreg cell differentiation in responding αβ T cells (Mora et al., 2008; Figure 1). Of interest, VDR-deficient mice do not show gross abnormalities in T cell compartmentalization. Collectively, it is reasonable to assume that the control of tissue-homing properties in T cells is more complex than previously appreciated.

EFFECTOR VERSUS MEMORY T CELLS

Effector T cells, i.e., activated, short-lived T cells generated during the onset of immune responses, not only travel to the tissue in which the DCs have captured and processed the cognate antigens, but disperse widely to other non-involved organs as well (Reinhardt et al., 2001; Liu et al., 2006; Brinkman et al., 2008). By doing so, effector T cells may forestall dissemination of infectious agents to other sites, but from the standpoint of homing, it means that a particular tissue tropism induced during contact with tissue-derived DCs does not override alternative trafficking routes. This indicates that in early immune responses redundancy, as opposed to selectivity, is an essential element of protective immunity. As such, we hypothesize that memory T cells (i.e., resting, long-lived T cells that survive the T cell contraction phase) are the ones that preferentially respond the tissue-selective localization cues.

HOMEOSTATIC VersUS INFAMMATORY T CELL TRAFFIC

During inflammation, the main goal of the infected tissue is to recruit as many effector immune cells as possible. To do so, the local release of inflammatory mediators in conjunction with pathogen-derived products trigger an inflammatory cascade that results in the release of inflammatory chemokines and the expression of inducible adhesion molecules on microvascular endothelial cells. Inflammatory chemokines generally act on a large array of target cells and show a significant amount of redundancy in the recruitment of effector cells. As such, it is unclear to what extent tissue-selective homing mechanisms support the inflammatory chemokine-driven recruitment of effector cells. We postulate that tissue-selective immune cell homing operates under steady-state conditions and, thus, correlates with the tissue distribution and/or retention of resting memory cells. In the following section, we discuss human skin as a site with specific needs for immune protection and summarize the literature dealing with cutaneous chemokines.

CHEMOKINES PRESENT IN HUMAN SKIN

In the gut, it is clear that the constitutive and selective expression of CCL25 by intestinal epithelial cells recruits CCR9-expressing lymphocytes to the small intestine, but the question still remains as to whether a similar mechanism regulates the specific migration of long-lived memory lymphocytes to skin tissue. Previous data implicate CCR4, CCR6, and CCR10 in the recruitment of effectors to mucosal sites in inflammation, but as we discuss below, these receptors are unlikely to regulate homoeostatic migration. In order to identify potential candidates, one first needs to identify those chemokines that are expressed in skin and, much like CCL25 in the gut, are largely absent at other locations.

Numerous chemokines have been detected by various methods in human skin tissue (listed in Table 1) but few of these show skin-selective expression. Most skin chemokines are classified as inflammatory chemokines, meaning that they are upregulated under inflammatory conditions in order to target effector cells. Among those associated with inflammatory diseases are the CCR4 ligands CCL17 and CCL22. Both are produced by...
Table 1 | Chemokine expression in human skin.

| Chemokine | Receptor | Type | Method | Remarks |
|-----------|----------|------|--------|---------|
| CCL1      | CCR8     | Steady state | IHC/IF | Vascular EC of dermal plexus; LCs and melanocytes (Schaerli et al., 2004) |
|           |          |       | PCR/RNase/PA| Dermal vascular EC and resting Langerhans-type DC; activated mast cells, skin T cells and dermal fibroblasts (Schaerli et al., 2004; Gombert et al., 2005; Ebert et al., 2006; Hintzen, 2008) |
|           |          |       | IF     | Allergic contact dermatitis (Sebastiani et al., 2001; Gombert et al., 2005; Gros et al., 2009) |
| CCL17/CCL22| CCR4     | Steady state | PCR | Keratinocytes; dermal fibroblasts stimulated by inflammatory cytokines (Vestergaard et al., 2000; Albanesi et al., 2001; Horikawa et al., 2002; Yu et al., 2002; Fukuda et al., 2003; Sumiyoshi et al., 2003) |
|           |          |       | IF     | Keratinocytes; dermal fibroblasts stimulated by inflammatory cytokines (Vestergaard et al., 2000; Albanesi et al., 2001; Horikawa et al., 2002; Yu et al., 2002; Fukuda et al., 2003; Sumiyoshi et al., 2003) |
|           |          |       | PCR/ELISA | Keratinocytes, dermal lymphatic EC (Wick et al., 2008) |
|           |          |       | PCR     | Constitutive low levels in basal epidermis; keratinocytes and dermal vascular EC (Charbonnier et al., 1999; Homey et al., 2000; Schmuth et al., 2002) |
|           |          |       | IF     | Memory T cell arrest on activated dermal EC (Fitzhugh et al., 2000; Ghannam et al., 2011) |
| CCL20     | CCR6     | Steady state | PCR/ELISA | Keratinocytes, melanocytes, dermal vascular and lymph. ECs and fibroblasts upon stimulation with inflammatory mediators (cytokines, TLRs, SAGeC, anti-microbial peptides, or allergens (Dieu-Nosjean et al., 2000; Homey et al., 2000, 2007; Kriehuber et al., 2001; Nakayama et al., 2001; Tomiyama et al., 2001; Schmuth et al., 2002; Giustizieri et al., 2004; Meller et al., 2005; Tohyama et al., 2001; Schmuth et al., 2002)) |
|           |          |       | PCR     | Mycosis fungoides; cutaneous GVHD (Schmuth et al., 2002) |
|           |          |       | IF     | Behcets and AGEP (Keller et al., 2005) |
|           |          |       | PCR     | Langerhans cell histiocytosis (Annels et al., 2003; Fleming et al., 2003) |
|           |          |       | IF     | Lesions of lyme borreliosis (Mullegger et al., 2007) |
|           |          |       | PCR/ELISA | Drug-induced maculopapular exanthema (Fernandez et al., 2008) |
| CCL27     | CCR10    | Steady state | PCR/ELISA | Primary basal keratinocytes (Morales et al., 1999; Homey et al., 2000, 2002; Humphreys et al., 2005; Meller et al., 2005) |
|           |          |       | PCR/Northern/PCR | Podoplanin-low dermal lymphatic EC (Wick et al., 2008) |
|           |          |       | Northern/PCR | Generally induced by IL-1β and TNF-α; inhibited by prostaglandin E2 (Homey et al., 2000, 2002; Kanda et al., 2004; Meller et al., 2005) |
|           |          |       | PCR     | AD and Psoriasis (Homey et al., 2002; Kakinuma et al., 2003a; Hijnen et al., 2004; Campanati et al., 2007) |
|           |          |       | PCR     | Drug-induced maculopapular exanthema (Tapiag et al., 2004; Fernandez et al., 2008) |
|           |          |       | PCR     | Skin lesions of systemic sclerosis (Hayakawa et al., 2005) |
|           |          |       | PCR     | Cutaneous lupus erythematosus (Meller et al., 2005) |
|           |          |       | PCR     | Skin-affected GVHD (Faaia et al., 2006) |
|           |          |       | PCR     | Infections (Haemophilus ducreyi; Staphylococcus aureus; Humphreys et al., 2005; Holland et al., 2009) |
|           |          |       | PCR     | ATLL skin lesions (Harasawa et al., 2006) |
|           |          |       | PCR     | Malignant skin tumors (Kai et al., 2011; not confirmed in Pivarcsi et al., 2007) |

(Continued)
| Chemokine | Receptor | Type               | Methoda                  | Remarks                                                                 |
|-----------|----------|-------------------|-------------------------|-------------------------------------------------------------------------|
| CCL28     | CCR10    | Steady state      | RNA dot blot/Northern   | Normal skin but at much lower levels than CCL27 (Pan et al., 2000)       |
|           |          |                   | Tissue culture          |                                                                         |
| CCL28     |          | Inflamed          | PCR/ELISA               | TNF-α + IL-1β-stimulated HaCaT (Kanda et al., 2005)                      |
|           |          |                   | PCR                     | ATLL skin lesions (Harasawa et al., 2006)                                |
| CXCL12    | CXCR4    | Steady state      | PCR/ISH/IHC/IF/WB       | Blood ECs of superficial dermal plexus, sweat glands, keratinocytes, DC/LC and fibroblasts (Pablos et al., 1999; Fedyk et al., 2001; Gombert et al., 2005; Avniel et al., 2006; Cipriani et al., 2006; Narducci et al., 2006; Chen et al., 2009) |
|           |          |                   |                         |                                                                         |
| CXCL14    | Unknown  | Steady state      | ISH/Northern/PCR/IHC    | Epidermis and squamous epithelium; blood EC; basal keratinocytes and dermal macrophages and mast cells (Frederick et al., 2000; Kurth et al., 2001; Schaerli et al., 2005; Meuter and Moser, 2008) |
|           |          |                   |                         |                                                                         |
| CXCL16    | CXCR6    | Steady state      | IHC/PCR                 | Keratinocytes and dermal EC upon activation with pro-inflammatory mediators (Scholz et al., 2007; Tohyama et al., 2007) |
|           |          |                   |                         |                                                                         |
| CX3CL1    | CX3CR1   | Steady state      | IHC/PCR/WB              | Migratory LC; TNF-α and IFN-γ-stimulated keratinocytes, dermal fibroblasts, dermal EC line (Papadopoulos et al., 1999; Raychaudhuri et al., 2001; Fahy et al., 2003; Chen et al., 2011) |
|           |          |                   |                         |                                                                         |

*Abbreviations: IHC, immunohistochemistry; IF, immunofluorescence; ISH, in situ hybridization; FC, flow cytometry; RNase PA, RNase protection assay; WB, Western blot.
*Abbreviations: AD, atopic dermatitis; ACD, allergic contact dermatitis; AGEP, acute generalized exanthematous pustulosis; ATLL, adult T-cell leukemia/lymphoma; CTCL, cutaneous T-cell lymphoma; EC, endothelial cells; GVHD, graft versus host disease; LC, Langerhans cells; pDC, plasmacytoid dendritic cell; SAg, superantigen; TLR, Toll-like receptor.

epidermal keratinocytes and dermal fibroblasts in response to inflammatory signals (Vestergaard et al., 2000; Albanesi et al., 2001; Horikawa et al., 2002; Fukuda et al., 2003), and are prominently associated with atopic dermatitis (Vestergaard et al., 2000; Goebeler et al., 2001; D’Ambrosio et al., 2002; Horikawa et al., 2002; Sebastiani et al., 2002; Uchida et al., 2002; Zheng et al., 2003; Echigo et al., 2004; Guttmann-Yassky et al., 2007; Gros et al., 2009; Kamsteeg et al., 2010), Psoriasis (Rottman et al., 2001), and cutaneous lymphomas (Ferenczi et al., 2002; Yoshie et al., 2002; Kakinuma et al., 2003b; Ishida et al., 2005). In
addition to skin, CCL17/22 have been detected at elevated levels in the lung mucosa of asthmatics (Panina-Bordignon et al., 2001; Bochner et al., 2003). Additionally, CCR4+ T cells have been identified in inflammatory conditions affecting the synovium (Leipe et al., 2010), lung (Panina-Bordignon et al., 2001; Nouri-Aria et al., 2002; Vijayanand et al., 2010), liver (Oo et al., 2010), peritoneum and appendix (Michelle L. McCully and Bernhard Moser, unpublished observations), indicating that CCR4 aids the non-selective migration of effectors to many inflamed sites. In mice, early studies implicated CCR4 as being critical for the migration of antigen-specific effector cells and Tregs to inflamed skin (Reiss et al., 2001; Campbell et al., 2007), but more recent studies found that skin inflammatory responses were intact or even elevated in the absence of CCR4 expression (Lehtimaki et al., 2010; Sells and Hwang, 2010) underlining the significant amount of redundancy in the chemokine network during inflammation.

Similar to CCL17 (see above), CCL20, the single ligand of CCR6, is barely detectable in healthy skin but increases substantially with inflammation (Charbonnier et al., 1999; Homey et al., 2002; Schmuth et al., 2002). Increased CCL20 expression has been detected in several cutaneous inflammatory disorders (Table 1), notably Psoriasis (Charbonnier et al., 1999; Schmuth et al., 2002; Gombert et al., 2005; Keller et al., 2005; Kim et al., 2007). Relevant to the present discussion, CCL20 (as well as CCL17), have been detected at low levels in normal skin. CCL20 expression in the epidermis and on lymphatic endothelium has been proposed to regulate the constitutive migration of CCR6+ LCs and DC precursors (Charbonnier et al., 1999) whereas CCL17 expression in dermal blood vessels was suggested to facilitate trans-endothelial migration of circulating CCR4+ cells (Campbell et al., 1999; Chong et al., 2004).

A prominent role for CXCL12 in skin-selective homing of immune cells is unlikely due to its ubiquitous tissue distribution and the fact that its specific receptor CXCR4 is expressed on all circulating leukocytes. Evidence for a role of the membrane-bound chemoattractant CXCL16, the single ligand for CXCR6, in human skin immunity is relatively recent and includes constitutive expression on keratinocytes, and blood endothelia (Scholz et al., 2007; Tohyama et al., 2007). However, its expression is substantially increased in response to pro-inflammatory stimuli and, in addition to skin, CXCL16 is found in healthy lung parenchyma as well as inflammatory sites within the lung (Morgan et al., 2005), liver (Heydtmann et al., 2005), and colon (Diegelmann et al., 2010), precluding its involvement in tissue-selective homing. A second membrane-bound chemoattractant, CX3CL1, the single ligand for CX3CR1, was originally found in the epidermis (Papadopoulos et al., 1999; Sugaya et al., 2003); however, using a more selective antibody reagent, expression of CX3CL1 in healthy skin could not be confirmed (Lucas et al., 2001; Echigo et al., 2004), whereas its expression was readily detected in many cutaneous inflammatory lesions (Fraticelli et al., 2001; Raychaudhuri et al., 2001; Sugaya et al., 2003; Echigo et al., 2004; Hasegawa et al., 2005; Izraely et al., 2010; Nakayama et al., 2010).

This leaves three potential chemokine candidates, CCL27, CCL1, and CXCL14, for regulating the trafficking of skin-homing lymphocytes. CCL27 is selectively produced by epidermal keratinocytes and controls the migration of CCR10+ T cells to the epidermal compartment (Morales et al., 1999; Sigmundsdottir et al., 2007). In blood of healthy donors, CCR10+ T cells make up a significant proportion of CLA+ T cells (Hudak et al., 2002), whereas in healthy skin, CCR10+ cells were not detected (Michelle L. McCully and Bernhard Moser, unpublished observations), arguing against a role for CCL27 in controlling cutaneous T cell traffic under steady-state conditions. Epidermal CCL27 production is significantly increased in response to inflammatory mediators and is prominently present in cutaneous inflammatory lesions (listed in Table 1). In support of an inflammatory role, CCL27–CCR10 was found to regulate T cell recruitment to the epidermis in mouse models of acute skin inflammation (Reiss et al., 2001; Homey et al., 2002). Of interest, CCR10+ cells are also targeted by CCL28, which is widely expressed by many mucosal tissues (Pan et al., 2000), which were shown to harbor CCR10+ T cells, and B cells (Eksteen et al., 2006; Morteau et al., 2008), arguing against a contribution to a skin-selective address code.

CXCL14 and CCL1 are two chemokines that are readily detected in healthy human skin. CCL1 and its receptor CCR8 are discussed separately in the next chapter. CXCL14 is constitutively expressed in epidermal and squamous epithelial tissues (Meuter and Moser, 2008). In skin, CXCL14 is mainly produced by basal keratinocytes, but expression has also been detected on dermal endothelial cells, macrophages, and mast cells (Kurth et al., 2001; Schaeeri et al., 2005; Meuter and Moser, 2008). Of note, the production of this chemokine by keratinocytes was very high, allowing for its purification from natural sources in quantities large enough for functional studies. The receptor for CXCL14 has yet to be identified, but chemotaxis assays have implicated CXCL14 in the specific mobilization of monocytes (Kurth et al., 2001), NK cells (Starnes et al., 2006), and human, but not mouse, dendritic cell precursors (Schaeri et al., 2005; Starnes et al., 2006; Meuter et al., 2007). CXCL14 does not act on T cells and, therefore, does not play a role in controlling immune surveillance T cells in healthy human skin. Numerous additional inflammatory chemokines not listed in Table 1 are also known to be produced in diseased skin, but have been excluded here as they are known to be produced in many other inflamed tissues and thus, cannot account for skin-specific immune cell traffic.

**DOES CCL1–CCR8 PLAY A ROLE IN SKIN IMMUNITY?**

Today, CCL1–CCR8 is one of the least understood chemokine system despite the fact that CCL1 (formerly known as I-309 and TCA3 in human and mouse, respectively) was the first among a long succession of CC chemokines to be discovered (Burd et al., 1987; Miller et al., 1989). The cDNA cloning strategy, based on RNA extracted from human and mouse T cells, already indicated that CCL1 may target T cells; and activated T cells secrete up to large amounts of CCL1, whereas its production by tissue cells appears to be less prominent (Table 2). CCL1 is not a bonafide inflammatory chemokine since its expression in the presence of inflammatory stimuli is controversial. Besides activated T cells, human immune cells reported to produce CCL1 mRNA, and/or protein include mast cells and DCs. In skin, CCL1 is produced by cultured T cells.
Table 2 | Expression of human CCL1 and CCR8.

| Expression      | Method                   | Remarks                                                                 |
|-----------------|--------------------------|-------------------------------------------------------------------------|
| CCL1 T cells    | mRNA, ELISA              | Original cloning (Miller et al., 1989); in vitro Th1 and Th2 cells (Sallusto et al., 1999); skin-derived T cells (Schaerli et al., 2004) |
| Monocytes       | mRNA, immunoprecipitation| Cultured blood monocytes (Selvan et al., 1997)                           |
| dendritic cells |                          |                                                                         |
| Mast cells      | mRNA, IHC, ELISA,        | Activated, cord blood-derived (Nakajima et al., 2002; Gonzalez et al., 2007); mast cell leukemia (Selvan et al., 1994) |
| Keratinocytes   | mRNA                     |                                                                         |
| Endothelial cells| IHC, western blot        | Activated HUVEC (Haque et al., 2000); skin endothelial cells (Gombert et al., 2005) |
| Thymus          | IHC                      | Macrophages, epithelial cells (Annunziato et al., 2002)                 |
| Skin            | mRNA, IHC, ELISA         | LC, melanocytes, endothelial cells in healthy skin (Schaerli et al., 2004); LC, mast cells, endothelial cells in atopic dermatitis (Gombert et al., 2005); nickel allergy (Sebastiani et al., 2001) |
| Lung asthma, allergy | mRNA, IHC, ELISA    | Bronchial epithelial cells, BALF (Montes-Vizuet et al., 2006); epithelial cells following RSV infection (Zhang et al., 2001); but not found in diseased lung (Panina-Bordignon et al., 2001; Bochner et al., 2003; Ying et al., 2008) |
| CCR8 T cells    | Flow cytometry, function | CD4<sup>+</sup> > CD8<sup>+</sup> T cells, Foxp3<sup>+</sup> Treg, Th2 and other blood CD4<sup>+</sup> T cells (Soler et al., 2006); low numbers on CLA<sup>+</sup> cells (Clark et al., 2006); subset of PBL but no function (Gombert et al., 2005); CD4<sup>+</sup> > CD8<sup>+</sup> blood T cells, Th2 cells (Mutalithas et al., 2010) |
| Treg cells      | mRNA, function           | Cutaneous nickel-specific CD4<sup>+</sup> Treg cells (Sebastiani et al., 2001); blood CLA<sup>+</sup>, CD4<sup>+</sup>CD25<sup>+</sup> T cells (Iellem et al., 2001; Colantonio et al., 2002a) |
| Th2             | mRNA, function           | Th2 clones and lines, upregulation during short-term activation (D’Ambrosio et al., 1998; Zingoni et al., 1998; Colantonio et al., 2002b); upregulation during late Th2 differentiation (Colantonio et al., 2002b); IL-5 producing Th2 cells (Islam et al., 2011) |
| Thymocytes      | mRNA, flow cytometry     | CD4<sup>+</sup> > CD8<sup>+</sup> (Napolitano et al., 1996; Zaballos et al., 1996; Tiffany et al., 1997; Zingoni et al., 1998) Natural Treg cells (CD4<sup>+</sup>CD25<sup>+</sup>, CD8<sup>+</sup>CD25<sup>+</sup>; Annunziato et al., 2002; Cosmi et al., 2003) |
| NK cells        | mRNA, flow cytometry, function | No expression and response to CCL1 of blood NK cells (Loetscher et al., 1996); but functional expression in IL2 act. NK cells (Inngjerdingen et al., 2000, 2001); on skin but not blood NK cells (Ebert et al., 2006) |
| Monocytes       | mRNA, functional Flow    | Chemotaxis (Miller and Krangel, 1992); and mRNA expression on blood monocytes (Tiffany et al., 1997); not confirmed by (Napolitano et al., 1996; Samson et al., 1996; Roos et al., 1997); monocyte subsets, monocyte-derived DC and LC but no function (Haque et al., 2000; Qu et al., 2004; Gombert et al., 2005) |
| dendritic cells | cytotometry               |                                                                         |
| Lung asthma, allergy | IHC, flow cytometry   | Bronchial CD4<sup>+</sup>T cells (Panina-Bordignon et al., 2001; Gonzalez et al., 2007); not confirmed in asthmatics (Ying et al., 2008); low on BAL Th2 cells (Mutalithas et al., 2010) |
| Skin            | Flow cytometry            | CLA<sup>+</sup>, mostly Th1 cells (Clark et al., 2006); primary skin αβ T cells, γδ T cells and NK cells (Schaerli et al., 2004; Ebert et al., 2006) |

as well as LCs, possibly melanocytes and microvascular endothelial cells but not by keratinocytes or dermal fibroblasts (Schaerli et al., 2004). Its expression was also associated with atopic dermatitis, allergy, and asthma (Sebastiani et al., 2001; Zhang et al., 2001; Bochner et al., 2003; Ying et al., 2008). There is no evidence for CCL1 production by other tissues. Obviously, identification of CCL1 target cells is of paramount importance for understanding the role played by CCL1 in physiologic and/or pathologic conditions.

CCR8, the only receptor for CCL1, was cloned in the late 90s (Roos et al., 1997; Tiffany et al., 1997; Goya et al., 1998). Early mRNA expression and functional data pointed to CCR8 being expressed by diverse subsets of T cells, including Th1, Th2, Treg cells, and, interestingly, CD4<sup>+</sup>CD25<sup>+</sup> thymocytes with natural Treg function (Table 2). Expression and function of CCR8 in monocytes, DCs, and NK cells is still controversial and this is most likely due to paucity in CCR8-specific Abs. Some commercial Abs turned out to lack specificity or showed cross-reactivity with several chemokine receptors, which added to the confusion about the CCL1 target cells.

Mice with genetic modifications provide strong models for the in vivo study of chemokine systems. TCA3, the mouse orthologue of human CCL1, was originally cloned from activated T cells (Burd et al., 1987) and its receptor CCR8 was found to be expressed by lymphocytes from blood and thymus (Zaballos et al., 1996; Goya et al., 1998). The results from CCR8<sup>−/−</sup> mice are controversial.
Two studies demonstrate a role for CCR8 in the control of Th2 cells and eosinophils in models of allergic lung diseases (Chensue et al., 2001; Gonzalo et al., 2007), implicating mast cells as a source of CCL1. However, these findings were contested by the work of other laboratories (Chung et al., 2003; Goya et al., 2003; Mikhak et al., 2009). Although a role for CCR8 in antigen-driven lung disease remains unclear, an additional study has implicated CCR8 in contributing to the development of chronic inflammation in a model of chronic Aspergillus-induced asthma (Buckland et al., 2007). A separate line of studies has linked CCR8 signaling with protection of apoptosis in mouse thymocytes (Van Snick et al., 1996; Louahed et al., 2003; Spinetti et al., 2003), suggesting a role in thymocyte development (Kremer et al., 2001). A recent report highlights the importance of CCR8 in a mouse model of atopic dermatitis (Islam et al., 2011). However, it is important to note that in this model mouse CCL8, but not mouse CCL1, was identified as the physiologically relevant ligand for CCR8 involved in controlling Th2 mobilization, and subsequent skin allergy development. To complicate matters further, human CCL8 (alias MCP-2), one of four chemokines for CCR2, does not bind to human or mouse CCR8, highlighting fundamental differences in immune mechanisms between mice and humans. Collectively, mouse CCR8 marks a subset of Th2 cells with a potential role in allergic disease of lung and skin and, probably, a subset of thymic CD4+ T cells. An involvement of CCL1/CCL8 and CCR8 in gastrointestinal inflammation has not been reported.

The current state in research supports our view that CCR8 marks a functionally heterogeneous population of CD4+ and CD8+ T cells subsets featuring homing preferences for human skin (although lung homing properties cannot be excluded at present; Figure 2). Human skin is a vast reservoir for memory T cells under steady-state conditions, most of which express CCR8 (Table 3). Our previous work found that the majority of skin-resident CD4+ and CD8+ αβ T cells, (Vβ1+) γδ T cells, and a subset NK cells stained positive for this receptor (Schaerli et al., 2004; Ebert et al., 2006). Several reports have documented CCR8 expression on skin LDCs, DCs, and their mononuclear precursors (Haque et al., 2000; Qu et al., 2004; Gombert et al., 2005; Gros et al., 2009), but we were unable to confirm these findings.

**FIGURE 2 | CCR8+ T cells are part of the cellular immune surveillance system in healthy human skin.** This model describes the recruitment to the skin and retention of CCR8+ memory T cells (and possibly NK cells). The skin address code is composed of CLA, a ligand for E/P-selectins, and CCR8, the chemokine receptor for CCL1, both present on the luminal side of the microvasculature within the dermal plexus. Following trans-endothelial migration, dermal CCR8+ T cells sense CCL1 constitutively expressed by LDCs (and possibly melanocytes), and subsequent co-localization allows the screening of LDCs by CCR8+ T cells for the presence of cognate peptide-MHC molecules. Self-peptide-presenting LDCs may induce local Treg cell responses whereas microbial peptide-presenting LDCs may induce protective anti-microbial T cell responses. In this model, CCR8 does not distinguish between functional T cell subsets, but rather combines different T cell subsets that are necessary for immune surveillance of human skin in the steady state. Tps, peripheral surveillance T cell; EC, endothelial cell; Me, melanocyte; LC, Langerhans cell; CLA, cutaneous T lymphocyte antigen.
Despite being coined a marker for Th2 cells, CCR8-expressing, skin-derived CD4+, and CD8+ T cells were biased toward the production of the pro-inflammatory cytokines IFNγ, TNFα, and IL-2 after ex vivo stimulation, while the secretion of Th2-associated cytokines (IL-4, IL-5, and IL-13) were rarely detected (Schaerli et al., 2004; Clark et al., 2006). Additionally, CCR8-expressing CD8+ T cells were devoid of cytotytic functions, suggesting that CCR8+ T cells participate in local immune responses through the secretion of pro-inflammatory cytokines. The fact that skin–tropic viruses encode functional proteins targeting CCR8 further supports a role of CCR8 in skin-specific immune defense. Specifically, the human poxvirus molluscum contagiosum encodes a selective antagonist for CCR8, called MCI148 (Luttichau et al., 2000). And human herpes virus 8 (HHV8) encodes two viral orthologues of the macrophage inflammatory protein family (vMIP-I and vMIP-II); vMIP-I functions as a CCR8 agonist, while vMIP-II serves as a broad-spectrum chemokine receptor antagonist (Sozzani et al., 1998; Dairaghi et al., 1999; Endres et al., 1999).

Although CCR8 marked a significant proportion of skin-resident T cells in the steady state, CCR8+ T cells were at present not found (or were extremely rare) in many skin-associated inflammatory diseases (Schaerli et al., 2004; Gombert et al., 2005; Keller et al., 2005; Ottaviani et al., 2006; Gros et al., 2009). The relevance of this disparate expression (non-inflamed versus inflamed) is currently unclear but points toward a role for CCR8 and its ligand CCL1 in the localization of peripheral T cells and NK cells under steady-state conditions. This is supported by the presence of CCL1 expression on the dermal microvasculature as well as by epidermal Langerhans cells and melanocytes of healthy, non-inflamed, human skin. Importantly, we did not find CCL1 expression in keratinocytes or dermal fibroblasts; two cell types that mainly produce CXCL14 in the steady state and a multitude of inflammatory chemokines in response to infection. Based on these data, we propose a model whereby CCL1–CCR8 regulates the homeostatic homing of peripheral immune–surveillance T cells to human skin tissue (Figure 2). This model predicts that the presence of low levels of CCL1 on microvascular endothelial cells recruits CLA+ CCR8+ T cells to the dermis of healthy human skin. Expression of CCL1 by LCs and/or melanocytes may localize dermal CCR8+ T cells in close proximity of the epidermis. In fact, CCL1 production by LCs as opposed to the highly abundant keratinocytes (or dermal fibroblasts) fits nicely with the view of a continuous interaction between CCL1–CCR8+ memory T cells in the dermis and peptide–MHC-presenting LCs in the epidermis. By responding to self-peptide–MHC or microbial peptide–MHC molecules, dermal CCR8+ T cells would act as essential players in tissue homeostasis, and/or anti-microbial immunity. This model also extends to cutaneous γδ T cells and even NK cells, indicating that the principal role of CCL1–CCR8 may be to regulate the co-localization of immune surveillance cells in healthy skin that, collectively, guarantee skin tissue integrity.

**CONCLUDING REMARKS**

As discussed above, we propose that the single chemokine, CCL1, and its receptor CCR8 regulate the steady-state homing of long-lived lymphocyte populations to human skin tissue. The relationship between CCR8+ T cells in the skin and those in blood is not clear at present. However, we would like to portray the view that they differ fundamentally in terms of function. In support, in a mouse model of cutaneous HSV infection, HSV-specific memory T cells were shown to reside primarily in skin tissue as opposed to blood (Wakim et al., 2008; Gebhardt et al., 2009). Although similar studies cannot be done in humans, we, and others have shown that human skin–derived CCR8+ T cells are capable of producing many cytokines in response to stimulation with a bias toward the production of Th1 cytokines (Schaerli et al., 2004; Clark et al., 2006). On the other hand, blood CCR8+ T cells preferentially secrete Th2 type cytokines (Zingoni et al., 1998; Soler et al., 2006; Islam et al., 2011), most notably IL-5 (Zingoni et al., 1998; Soler et al., 2006; Islam et al., 2011). Furthermore, we wish to point out that in addition to γδ T cells, NK cells, and γδ T cells in healthy human skin also express CCR8, further underscoring the heterogeneity among CCR8+ cells. Clearly, further studies with primary lymphocytes from human skin are required to better define their function. It is essential that these studies be carried out using human tissue as mouse skin differs fundamentally in terms of physiology (i.e., fur, thickness, vitamin metabolism) as well as in the types of immune cells present (DETC cells in mice that are absent in humans). These studies also need to include experiments focusing on the generation of CCR8+ T cells during activation of naïve peripheral blood T cells with diverse subsets of DCs as the factors that induce CCR8 expression in T cells have yet to be defined. What does appear to be certain at this stage is that there exists significant phenotypic and functional heterogeneity among human skin CCR8+ lymphocytes, lending support to the model whereby CCR8 marks immune surveillance cells characterized by a distinct tissue tropism (skin) as opposed to a specific effector function.

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**Table 3 | CCR8 in cutaneous immune cells.**

| Cell type | Steady state | Range (%) | Reference |
|-----------|-------------|-----------|-----------|
| **LYMPHOCYTES** | | | |
| CD3+ T cells | + | (46–54)* | Clark et al. (2006) |
| CD4+ T cells | + | (26–74) | Schaerli et al. (2004) |
| CD8+ T cells | + | (59–95) | Schaerli et al. (2004) |
| γδ T cells | + | (46–60) | Ebert et al. (2006) |
| B cells | – | | Schaerli et al. (2004) |
| **NON-LYMPHOCYTES** | | | |
| NK cells | + | (<50) | Ebert et al. (2006) |
| Monocytes/macrophages | – | | Schaerli et al. (2004) |
| DCs | – | | Schaerli et al. (2004) |

*Combined ranges from all isolation techniques.
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