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REVIEW

Tissue-Specific Homing of Immune Cells in Malignant Skin Tumors

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Abstract Tissue-specific migration of immune cells involved both in physiological and pathological immune responses is a current research subject for medical science. Several homing molecules have been identified orchestrating extravasation of immune cells to certain peripheral non-lymphoid tissues such as gut, lung and skin. Regarding lymphocyte homing to skin, the first-line defense of human body cutaneous lymphocyte associated antigen (CLA) and a group of chemokine-chemokine receptor pairs are considered to be of crucial importance. The aim of the present review is to summarize existing knowledge about skin- and tumor-specific migration of immune cells playing a major pathogenetic role in host immune responses induced by non-lymphoid malignant skin tumors as well as in the development of primary cutaneous T-cell lymphomas (CTCL). Melanoma malignum, squamous and basal cell carcinoma evoke host immune responses and consequently a subset of reactive immune cells is recruited to site of the tumor. Regarding migratory process and exact functional role of these cells a growing number of data is available in literature. On the other hand tissue-specific immune cell homing is regarded as a key process in the pathogenesis of CTCL where malignant T-lymphocytes can be found in circulation and symptomatic skin. Hereby homing mechanism of malignant T-cells in mycosis fungoides and Sézary-syndrome as separate clinical entities of CTCL is discussed. A precise insight into the molecular background of skin- and tumor-specific immune cell migration can contribute to developing efficient vaccine therapies in non-lymphoid malignant skin tumors and beneficial treatment modalities in CTCL.

Keywords Lymphocyte homing receptors · Cutaneous lymphocyte associated antigen · Malignant melanoma · Basal cell carcinoma · Squamous cell carcinoma · Cutaneous T-cell lymphoma

Abbreviations

Tem	effector memory T lymphocytes
Tcm	central memory T lymphocytes
CLA	cutaneous lymphocyte associated antigen
PSGL-1	P-selectin glycoprotein ligand 1
DC	dendritic cells
TILs	tumor infiltrating lymphocytes
Treg cells	regulatory T cells
LFA-1	leukocyte function associated antigen 1
VLA-4	very late antigen 4
ICAM	intercellular adhesion molecule
VCAM	vascular cell adhesion molecule
VEGF	vascular endothelial growth factor
TGF	fibroblast growth factor
SCC	squamous cell carcinoma
iNOS	inducible NO synthetase
BCC	basal cell carcinoma
CTCL	cutaneous T cell lymphoma

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SS	Sézary-syndrome
MF	mycosis fungoides
SDF-1	stromal cell-derived factor 1

Introduction

Tissue-specific homing of immune cells is involved in both physiological and pathological immune mediated processes [1–4]. Homing properties of effector memory T-lymphocytes (Tem) are mostly under investigation as in case of antigen-rechallenge these cells are uniquely able to migrate in great numbers to a certain peripheral non-lymphoid tissue where they have previously encountered the antigen. Cytokines secreted by antigen presenting cells influence the expression of cell-surface homing markers on newly activated lymphocytes [5–8]. Regarding skin, the outermost barrier of human body the most specific homing molecule of Tem is known as cutaneous lymphocyte associated antigen (CLA) [6, 9–11]. CLA is a carbohydrate epitope of the cell surface protein P-selectin glycoprotein ligand 1 (PSGL-1) and binds E-selectin and P-selectin, both adhesion receptors expressed on endothelium of skin microvasculature [10, 12]. The expression of CLA is supposed to be strictly controlled. IL-12, a cytokine secreted by dendritic cells (DCs) and mediating Th1 differentiation of naiv T-cells is a major stimulatory factor of CLA expression in vivo. In contrast IL-4 promoting the Th2 pathway shows negative correlation with the rate of CLA expression [9]. However, CLA is not exclusively expressed on Th1 effector memory cells but also on Th2, Th17 lymphocytes and in a small percentage even on B-lymphocytes as well as peripheral monocytes and granulocytes [11]. In the local microenvironment of antigen presentation soluble molecules (eg. vitamin D, A) originating from skin or lymph node contribute to generation of the homing pattern [9, 13–15]. The co-expression of CLA and certain chemokine receptors is needed to a perfect skin migratory process. Chemokine receptors are expressed mainly on lymphocytes, monocytes, neutrophils and eosinophils. They selectively bind their matching chemokines, a group of small (~8-14 kDa), structurally related molecules that regulate tissue-specific migration of leukocytes [16]. Chemokine receptors expressed on skin-homing lymphocytes are attracted by chemokines produced in skin cells. Based on existing data, following chemokine receptor-chemokine pairs are involved in skin-specific migration of T cells: CCR4-CCL17, CCL22; CCR6-CCL20; CCR10-CCL27 and CXCR3-CXCL9, CXCL10, CXCL11 [5, 17, 18]. The migration happens through a stepwise process initiated by a highly specific but loose interaction between CLA and E-selectin. Their binding enables the chemokine mediated activation of several non-specific adhesion molecules on immune and endothelial cells resulting in a firm, irreversible adhesion, a subsequent extravasation and migration to the site of inflammation or malignant cell proliferation [9, 19, 20] (Fig. 1). Hereby we give a summary on details of this migratory process that might greatly determine the pathogenesis and the clinical outcome of malignant skin tumors including non-lymphoid neoplasias and certain forms of cutaneous T-cell lymphomas.

Tumor-Specific Homing of Immune Cells in Melanoma

It was postulated years ago that there is a selective accumulation of immune cells with a tumor- and tissue-specific phenotype in malignant skin tumors [21]. The presence of tumor infiltrating lymphocytes (TILs) in primary cutaneous melanoma was first described by Clark et al. in 1969 [22] (Fig. 2). Later several studies demonstrated a prognostic significance of the number of these cells. As increased number of TILs in the tumor mass and microenvironment could be connected to a better clinical outcome, it was supposed that all lymphocytes migrated to the tumor burden exert antitumor functions [23–26]. Subsequently it became obvious that TILs don't represent a homogenous group. Beside CD4+ and CD8+ conventional αβ T-lymphocytes, NK-cells and γδ T-cells, all with antitumor activity, also CD4+CD25+Foxp3+ regulatory T-cells (Treg-cells) are present in melanoma lesions. Treg-cells own immunoinhibitory properties and promote tumor progression by hampering tumor-associated reactive lymphocytes [27–30]. Weishaupt et al. examined molecular and cellular changes in metastasizing melanoma and suggested that increased number of Treg-cells found both within and near the tumorbed is a hallmark of tumor progression [31]. Based on these findings the prognostic role of TILs is not determined by their number but rather the complexity of their different functions [27].

Antitumor or tumor promoting function of TILs is initiated by their tissue- and tumorspecific recruitment to the tumor mass. This complex homing and transmigratory process is enabled by a certain group of adhesion molecules as well as skin- and tumorspecific homing receptors. Additionally, differences in TIL-homing to primary tumors and metastatic lesions are of special interest as advantage of T-cell adoptive cancer therapy, the most promising targeted immunotherapy, is mostly expected in advanced, metastatic melanoma [32–34].

Adams et al. analyzed the cell-surface phenotype of TILs cultured from human melanoma in order to understand their tumor-homing properties. They found a significant upregulation of the skin-homing receptor cutaneous lymphocyte associated antigen (CLA) which was proven to be independent from culture conditions and rather a characteristic feature of in vivo generated TILs [35]. Based on the finding

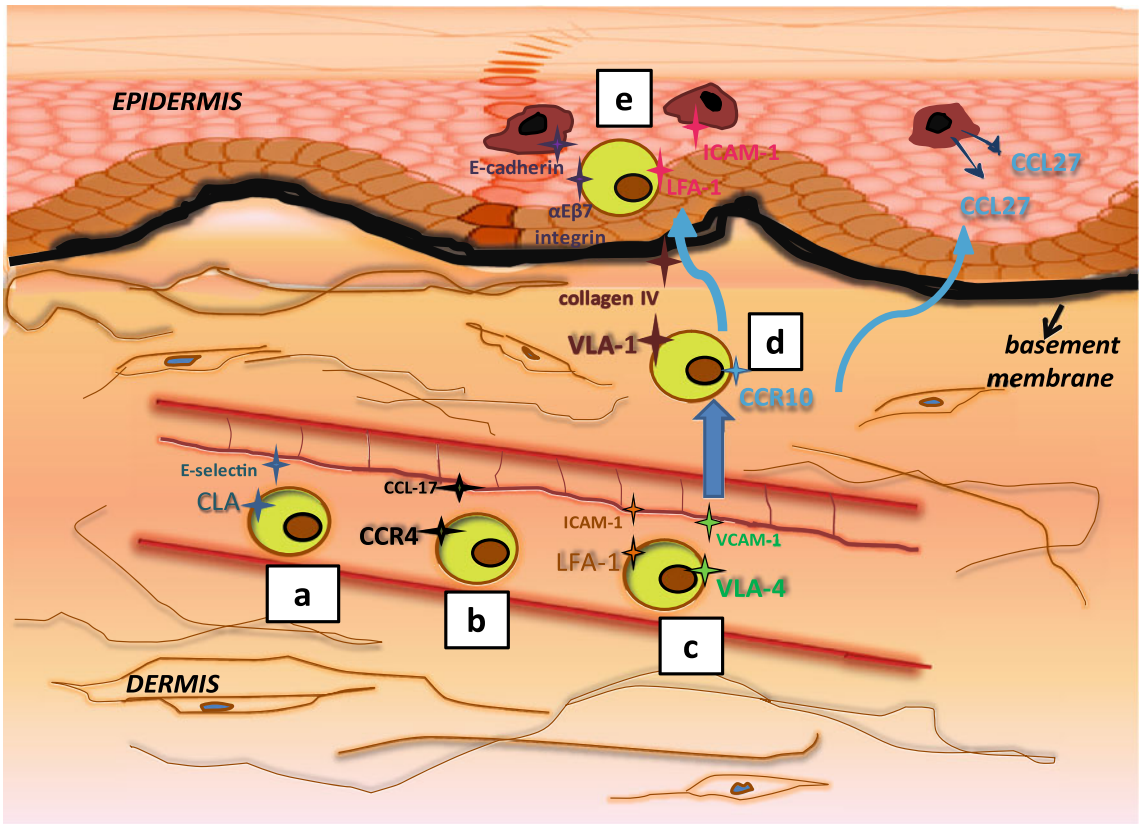

Fig. 1 Lymphocyte extravasation to the skin a) specific but loose CLA–E-selectin binding →ROLLING of T-cells along vessel wall b) binding of CCR4 (on T-cell) to CCL17 (on endothelial cell); coexpression of CLA and CCR4 on T-cells is responsible for skin-specific homing. c) LFA-1--ICAM-1, VLA-4--VCAM-1 binding (firm, but less specific interaction) → extravasation d) VLA-1 on T-cell binds to collagen IV of the basement membrane →T-cells migrate to the epidermis; CCR10+ T-lymphocytes are attracted to the epidermis by keratinocyte-secreted CCL27 e) cell-surface αEβ7 integrin on epidermal T-cells binds to E-cadherin on keratinocytes; LFA-1 on epidermal T-cells binds to ICAM-1 integrin on keratinocytes. → T-cells are captured in epidermis

that on melanoma vasculature there is a moderate expression of CLA-binding E-selectin, they suggested a role of the interaction of these two molecules in tumor-specific homing of TILs [35, 36]. Importance of the interaction between CLA and E-, P-selectin is underlined by several studies focusing on molecular differences between primary melanoma and advanced melanoma with metastases. Several authors found that the overall moderate expression rate of tumor endothelial adhesion molecules E- and P-selectin decreases over progression which in turn inhibits the migration of CLA+TILs to the tumor [31, 37, 38]. Beside the highly specific binding of CLA and E-, P-selectin other, less-specific adhesion molecule pairs also influence the homing ability of TILs. Microvasculature of metastatic melanoma can not upregulate adhesion molecules ICAM-1 (intercellular adhesion molecule) and VCAM-1 (vascular cell adhesion molecule) and is therefore less permeable to tumor-reactive lymphocytes expressing counter-ligands LFA-1 (leukocyte function associated antigen) and VLA-4 (very late antigen), respectively [39]. The expression of endothelial adhesion receptors might be modulated by VEGF (vascular endothelial growth factor) and TGF (tumor fibroblast growth factor) that are potent stimulators of angiogenesis [31, 40–42]. The lack of adhesion molecules on the tumor microvasculature can be a plausible explanation why Weishaupt et al. found T cells with an effector, lytic

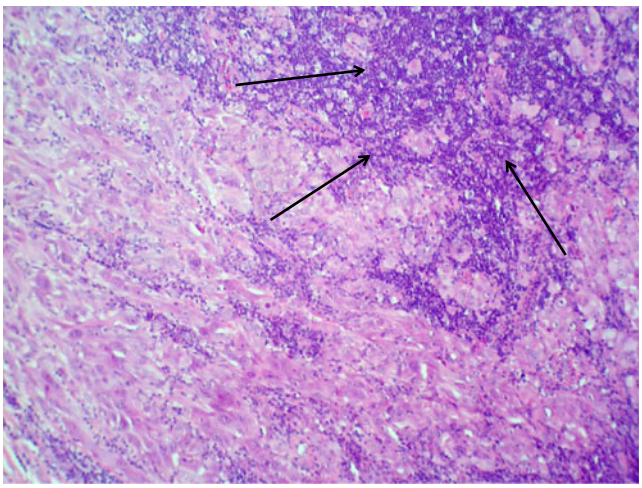

Fig. 2 Histopathological picture of melanoma malignum. Marking shows the presence of tumor infiltrating lymphocytes

function present in a small proportion in melanoma metastases and accumulated in great numbers in the closely surrounding tissue where in contrast a strong expression of the above mentioned adhesion receptors were noted. Similarly, mature antigen presenting dendritic cells with antitumor activity were localized to the peritumoral areas [31].

Gelb et al. found that CLA+T-lymphocytes are present in primary melanoma malignum, but they are undetectable in tumor metastases, including even cutaneous metastatic lesions. They supposed that only primary tumors (not cutaneous and extracutaneous metastases) are associated with the involvement (or irritation) of healthy epidermis which seems to be necessary to the recruitment of CLA+immune cells [21]. In inflammatory skin lesions keratinocytes secrete the cytokines TNF-α (tumor necrosis factor α) and IL-1 (interleukin-1) that are able to effectively upregulate the expression of CLA binding E-selectin on vascular endothelial cells, thereby promoting the skin-homing of inflammatory CLA+T cells. Additional keratinocyte expressed cytokines serve as chemoattractants for these T-lymphocytes [7, 21, 43]. Malignant tumor cells must lack some of these required soluble factors and tumor-specific CLA+lymphocyte accumulation is therefore possible only with the involvement of healthy but irritated epidermis [21]. The irritation is caused by epidermal invasion of the tumor cells that slightly damages surrounding healthy cells. This event leads to an inflammatory condition in primary tumors with the recruitment of immune cells that target malignant tumor cells [44]. Similarly, Weishaupt et al. found that T-cells trafficking to melanoma metastases are not bearing skin- and lymph node-specific homing receptors [31].

Several studies investigating host antitumor responses suggest that beside common and tissue-specific adhesion molecules also cytokines and chemokine-chemokine receptor pairs play an additional role in guiding of tumor infiltrating immune cells. Cytokine and chemokine synthesis is attributed to melanoma cells and additional cell types in the tumor microenvironment, such as macrophages, endothelial cells and recruited T-cells [45–48]. Key chemokines and corresponding chemokine receptors involved in the homing of melanoma infiltrating immune cells are summarized in Table 1. Angiostatic chemokines *CXCL9, 10, 11* recruit reactive Th1-lymphocytes expressing chemokine receptor CXCR3 [44, 49–51]. An associtation was demonstrated between strong expression of the chemokine CXCL9 and a great number of infiltrating T-lymphocytes in human malignant melanoma [52]. Graves et al. first described the production of chemokine *CCL2* by melanoma cells [53]. Secretion of *CCL5* by melanoma cells is suggested as a potential tumor escape mechanism as CCL5 was found to induce apoptosis of tumor infiltrating CD8+ T-lymphocytes [54]. Expression of *CCL20* in malignant melanoma leads to accumulation of mature DCs and effector T-cells in the tumor mass, thereby promoting antitumor host response [55].

In spite of the generally low number or absence of TILs in advanced-stage melanoma individual metastatic lesions occasionally can be rich in successfully migrated lymphocytes. One plausible explanation of this fact is that several oncogenic pathways (eg. Ras, B-Raf, Akt, Notch, Stat3) result in a malignant phenotype from the melanocyte lineage [45, 56–59]. The different signaling pathways can differently influence the expression of chemokine genes as well as other factors contributing to the tumor-specific migration of immune cells [45].

Mechanisms of Homing in Epithelial Skin Cancers (Squamous Cell Carcinoma, Basal Cell Carcinoma)

The hypothesis that effector and effector memory T-lymphocytes are important in controlling skin tumor growth is certified even by the fact that incidence of squamous cell carcinoma (SCC) is notably increased among transplant recipients on immunosuppressive therapy. Even therefore it is of special interest why also tumor reactive T-cells in patients with manifested SCC and without immunosuppression are unable to inhibit tumor manifestation [60]. A possible explanation is the significant downregulation of vascular E-selectin in human SCC and consquently, the failure of antitumor CLA+T-cells to sufficiently migrate to the tumor tissue – a similar event as observed in advanced melanoma. NO (nitric oxide) secreted by iNOS (inducible nitric oxide synthase)-expressing dendritic cells within tumorbed might contribute to impaired ability of endothelial cells to express E-selectin [61]. However, Hald et al. found that head and neck SCC contains numerous T-lymphocytes with the predominance of CD8+ cytotoxic T-cells [62]. In the study of Clark et al.[62] more than 50 % of the infiltrating T-cells were CD4+CD25+Foxp3+ Treg-cells suppressing antitumor effector lymphocytes. As a difference from normal Treg cells they lacked the expression of skin addressins CLA and CCR4 while expressed lymph node homing markers (L-selectin, CCR7) and resembled the central memory T-cell phenotype this way. However, SCC vessels expressed neither L-selectin ligands nor the chemokine pairs of CCR7 (CCL19, CCL21) [61]. Now tumor cells are considered to elaborate certain chemotactic factors that specifically attract Treg cells [27, 63]. Figure 3 shows histopathological picture of SCC with the presence of TILs.

Regarding immune cell infiltration of basal cell carcinoma (BCC) only a limited amount of data is available in the literature. Successful administration of topically applied immune response modifier imiquimod induced to get more attention on the topic of potential host immune response mechanisms in this semimalignant skin tumor. Tumor cells

Table 1 Main chemokines and corresponding chemokine receptors involved in immune cell infiltration of melanoma malignum

Chemokines	Corresponding chemokine receptors	Recruited immune cells due to binding of chemokine-chemokine receptor (under physiological/inflammatory conditions)	Special importance of chemokine-chemokine receptor binding in melanoma malignum
CCL2	CCR2	Th1, Th2, CD8+ CTL, NK-cells, monocytes, DC, iDC("inflammatory"conditions, eg. atherosclerosis)	tumor promoting role: recruitment of myeloid suppressor cells, consequent inhibition of reactive immune cells; accumulation of monocytes/ macrophages: angiogenesis, matrix degradation tumor inhibiting role: recruitment of reactive, inflammatory immune cells with antitumor function
CCL3	CCR1	iDC, T-cells, NK-cells, monocytes/macrophages (adhesion to activated vascular endothelium, transendothelial migration; allograft rejection; granuloma formation)	migration of tumor infiltrating immune cells with antitumor properties to the melanoma tumor mass
	CCR5	naive CD8+, CD8+ CTL, Th1, Treg, NK-cells,	tumor promoting role: angiogenesis, metastases tumor inhibiting role: recruitment of tumor infiltrating immune cells with antitumor properties
CCL4	CCR5	DC, iDC (recruitment of immune cells to infectious foci, viral infections, developing granulomas; mainly cellular immune response enhancement)	
CCL5	CCR5		enhancement of tumor progression by inducing apoptosis of tumor infiltrating lymphocytes
	CCR1	iDC, T-cells, NK-cells, monocytes/macrophages (mainly promoting Th1 mediated inflammatory cellular immune responses; granuloma formation)	accumulation of immune cells with antitumor properties in the tumor mass
	CCR3	T-cells, monocytes, DC, neutrophils, eosinophils (inflammatory immune responses, eosinophil recruitment in atopic dermatitis)	migration of immune cells with antitumor properties to the tumor mass
CCL17	CCR4	skin-homing CD4+ T-cells (Th2, Th17, Treg) (skin-specific migration under homeostatic and inflammatory conditions)	migration of skin-homing T-cells to the tumor mass (both inflammatory and regulatory T-lymphocytes involved)
CCL20	CCR6	Th17, B-cells, iDC, Treg (lymphorganogenesis, inflammatory immune responses)	migration of iDC that contribute to efficient antitumor response after maturation; recruitment of regulatory T-cells with tumor promoting function
CCL22	CCR4	skin-homing CD4+ T-cells (Th2, Th17, Treg) (skin-specific migration under homeostatic and inflammatory conditions)	migration of skin-homing T-cells to the tumor mass (both inflammatory and regulatory T-lymphocytes involved)
CCL27	CCR10	skin-homing CD8+ and CD4+ T-cells (skin-specific migration under homeostatic and inflammatory conditions)	migration of skin-homing antitumor T-lymphocytes to the tumor mass
CXCL9	CXCR3	Th1, Th17, CD8+ T-cells, NK-cells	tumor promoting role: development of metastases tumor inhibiting role: accumulation of inflammatory T-cells with antitumor function; angiostatic effect
CXCL10	CXCR3	(infection provoked inflammation; inflammatory skin diseases; allograft rejection; atherosclerosis)	
CXCL11	CXCR3		

DC dendritic cells, *iDC* immature dendritic cells, *NK-cells* natural killer cells, *Th1* T helper 1, *Th2* T helper 2, *Th17* T helper 17, *CTL* cytotoxic T-lymphocytes, *Treg* regulatory T-cells

of BCC often express HLA class I molecules and are immunogenic this way [64]. Similar to melanoma and SCC there is a significant downregulation of adhesion molecules in tumor microvasculature that results in decreased ability of immune cells to migrate to the tumor burden [65–68]. Multiple action of imiquimod contains enhanced expression of ICAM-1 on tumor endothelial cells mediated by upregulated proinflammatory cytokines (eg. IL-1, TNF-α, IFN-γ) [65, 69]. According to several investigatory results early cellular response after imiquimod treatment includes infiltration of mostly CD4+ T-lymphocytes, activated dermal dendritic cells and macrophages [70–72]. CD8+ T-cells appear only in a later phase and they are suggested to be rather suppressor than cytotoxic cells [70, 71]. Urosevic et al. reported the predominance of CD4+ T-cells before treatment and a reversal of CD4/CD8 ratio after imiquimod therapy, proposing a substantial role of infiltrating CD8+ T-cells in tumor elimination [65]. In BCC a significant number of CD4+ CD25+Foxp3+ Treg-cells and immature dermal dendritic cells was found surrounding the tumor bed, suggesting that

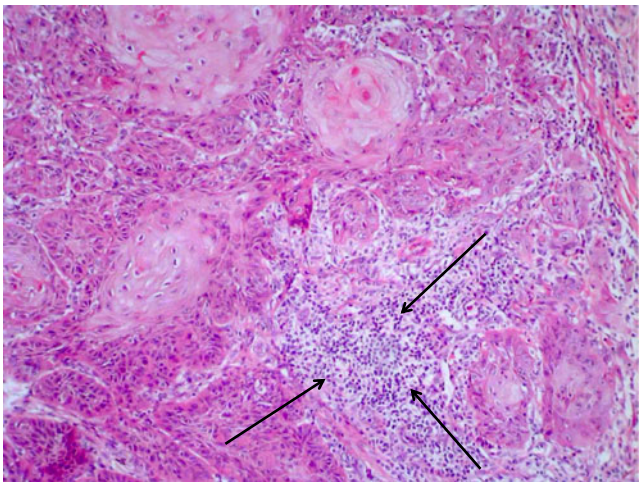

Fig. 3 Histopathological picture of squamous cell carcinoma. Marking shows the presence of tumor infiltrating lymphocytes

they contribute to insufficient anti-tumor response. The expression of CCL22, a Treg chemokine is also enhanced compared to normal skin.[73]

Skin-Homing of Malignant Lymphocytes in Primary Cutaneous T-cell Lymphomas: Mycosis Fungoides and Sézary-Syndrome

Cutaneous T-cell lymphomas (CTCL) represent a heterogenous group of non-Hodgkin lymphomas with the common presence of transformed skin-homing T-cells. Mycosis fungoides (MF) and Sézary-syndrome (SS) are epidermotrop variants of CTCL. Phenotypic features and origin of CTCL-cells are of special importance as they are regarded to greatly determine functional and migratory abilities of malignant lymphocytes.

Regarding *phenotypic* characteristics transformed lymphocytes generally exhibit a Th2 phenotype – supported by their secreted cytokine profile (eg. IL-4, IL-5, IL-10, IL-13) and expression pattern of cell-surface chemokine receptors (CCR4). However, the observation that SS and advanced-stage MF is often associated with clinically evident immunosuppression, raised the question whether proliferating CTCL-cells can originate from lymphocytes with Treg-cell phenotype that repress healthy immune cells [74–76]. Due to current data in early-stage *MF* there is a significant skin infiltration of normal Treg-cells and Th1 reactive lymphocytes that control the growth of CTCL-cells secreting mainly Th2 cytokines [74, 77, 78]. In fairly advanced disease there is a significant decrease in the amount of all types of cytokines which may refer to a Treg phenotype of tumor cells. As malignant Treg-cells CTCL-cells don't secrete many cytokines and suppress the productive capacity of reactive lymphocytes as well. However, whether tumor T-cells are derived from skin-homing Treg-cells or CD4+ Th2 memory cells that gain Treg-like functions over progression is still a matter of debate [77]. *SS* as a highly aggressive form of CTCL is consistently Th2 predominant, although several authors suggested a Treg phenotype of Sézary-cells [79–81]. Recently CD158k/KIR3DL2 (member of MHC class I antigen receptors) has been suggested to be a highly specific marker for Sézary-cells [82].

In connection with the *origin* of CTCL-cells novel evidence suggests that MF and SS are diverse presentations of CTCL [77, 83, 84]. Although sharing several molecular pathways important in the pathogenesis, they fundamentally show different clinical behaviour which is presumably the consequence of the fact that they arise from distinct T-cell lines with different homing abilities [20, 83].

MF is characterized by skin-localized patches and infiltrated plaques as well as a favorable clinical outcome [83, 85, 86]. Skin-infiltrating malignant T-cell clones express huge amounts of skin addressins CLA and CCR4 [83]. This cell surface pattern is combined with the lack of lymph node homing markers L-selectin and CCR7, a phenotype suggestive of effector memory lymphocytes (Tem) [20, 78, 83]. Mature Tem-cells generally migrate in a tissue-specific manner and stay permanently in peripheral non-lymphoid tissues without circulating in the blood flow and entering lymph nodes [5, 8, 83]. In the skin they seem to be restricted to fixed locations and secrete inflammatory cytokines recruiting reactive lymphocytes to the site of inflammation. This character has the consequence that in MF patients accumulation of malignant Tem-cells confined to the skin results in stable, inflamed skin lesions persisting for a long time at particular anatomic sites, without involvement of peripheral circulation and a consequent clinical progression [78, 83]. Krieg et al. suggested that in case of progression MF cells lose skin-homing properties and selectively upregulate lymph node homing marker CCR7 [44].

SS is associated with a poor prognosis that seems to be explained by the origin of transformed cells. *Circulating* tumor cells in SS express high levels of skin-specific chemokine receptor CCR4 but variable amounts of skin-homing markers CLA, CCR6 and CCR10 [83]. They universally coexpress lymph node addressins L-selectin and CCR7, consistent with a central memory phenotype [20, 83, 87–89]. Chemokines attracting CCR7+ lymphocytes are CCL19 and CCL21, constitutively synthesized in lymph nodes [20, 87]. Central memory T-cells (Tcm) usually circulate in the blood flow and regularly visit peripheral lymph nodes. A subset of them migrate even to peripheral non-lymphoid tissues, eg. the skin in a tissue-specific manner [5, 8, 83]. That might be the reason for the detectable number of tumor cells in circulation, the lymphadenopathy and the diffuse erythrodermic skin involvement seen in SS patients [83]. *Skin infiltrating* malignant lymphocytes in SS were

found to express skin-homing markers CLA and CCR4 in a significant percentage which seems to be necessary for the migration to cutaneous areas [83, 90]. A correlation was demonstrated between increased numbers of circulating CLA+lymphoma cells and extent of cutaneous lesions [91, 92].

Skin localization of CTCL-cells is collectively thought to be the consequence of several tissue-specific adhesion molecule pairs such as CLA and E-selectin as well as certain chemokines and chemokine receptors. Chemokine receptors expressed on skin-homing tumor cells enable a directed migration to chemokines produced by epidermal keratinocytes, endothelial cells and epidermal/dermal dendritic cells. Chemokines additionally lead to activation of integrins on leukocytes and their receptors on endothelial surfaces, thereby enabling a firm adhesion and transmigration of malignant lymphocytes to cutaneous tissues [87, 93–95] (Table 2).

Chemokine receptor *CCR4* is highly expressed on CTCL-cells [20, 74, 87, 96]. Corresponding chemokine ligands of CCR4 are *CCL17* and CCL22 [87, 97]. CCR4 was found to be highly expressed on neoplastic Th2 cells mostly in tumor stage of *MF* [98–100]. In accordance with high CCR4 expression of malignant lymphoma cells in advanced-stage MF *Kakinuma* et al. demonstrated a strong correlation between serum CCL17 levels and disease activity [99]. CCR4+ CTCL-cells form conjugates with CCL17 secreting dendritic cells in MF. These epidermal conjugates known as „Pautrier's microabscesses" are specific histopathological markers for MF [74, 87]. Several authors reported that CCR4 is present on circulating and skin-homing CLA+ CD4+ CTCL-cells in *SS* [89, 94, 95, 100, 101].

Similar to CCR4, *CCR10* is frequently expressed on CLA+skin-homing CTCL-cells [20, 74, 84, 87]. *CCL27* is the specific chemokine of CCR10 [87, 102]. Serum levels of CCL27 are increased in *MF*/*SS* patients and similar to CCL17 are suggested as a marker of disease activity [103, 104].

Based on their experimental data Hoeller et al. presumed that key chemokines directing CTCL-cells to skin are involved in different steps of the homing process. CCL17 seems to mediate firm arrest of tumor cells in dermal microvasculature, whereas CCL27 might play a role in the transmigration [94].

Chemokine receptor *CXCR3* and its corresponding ligands *CCL9*, *CCL10*, *CCL11* are involved in skin-homing of CTCL-cells. A high percentage of CXCR3+ malignant lymphocytes is present in early-stage *MF*. CXCR3+ tumor cells are mostly absent in advanced stages, consistent with the hypothesis that altered chemokine receptor expression and decreased skin-homing ability of tumor cells result in clinical progression in MF [84, 102, 105–107]. Fierro et al. reported low expression of CXCR3 on CTCL-cell in *SS* [101] while Notohamiprodjo et al. could detect a strong expression in all biopsy samples from SS patients [84].

Chemokine receptor *CXCR4* is also regarded to play a role in homing of CTCL cells [86, 87, 101, 102]. *CXCL12*, the counter-ligand of CXCR4 is usually cleaved and inactivated by the T-cell membrane-bound protease CD26. Circulating and even skin-infiltrating CTCL cells are characterized by the loss of CD26, which may contribute to their CXCR4 mediated skin recruitment and accumulation [86, 87].

Table 2 Key chemokine receptors and corresponding chemokines involved in skin- homing of CTCL-cells

Chemokine receptors	Chemokines
CCR4	CCL17, CCL22
CCR10	CCL27
CXCR3	CXCL9, CXCL10, CXCL11
CXCR4	CXCL12

Conclusion and Future Perspectives

Immune cell infiltration and function in malignant skin tumors is a complex process regulated by numerous cell types and several contributing factors in tumor microenvironment.

TILs in non-lymphoid malignant skin tumors exert variable functions and their homing requires tissue-specific homing and adhesion molecules as well as chemokine-chemokine receptor pairs. CLA expressed on skin-homing TILs and its corresponding endothelial receptors are regarded as key molecules in this migratory process. In metastatic lesions downregulation of CLA-binding selectins results in decreased amount of tumor infiltrating CLA+ reactive lymphocytes. This molecular change is of special importance in adoptive cancer therapy of metastatic melanoma, where isolated tumor reactive CD8+ T-cells are in vitro expanded and reinfused to the patient: Changes in the homing ability of TILs can greatly hamper the effectiveness of this targeted immunotherapy as reinfused lymphocytes are needed to successfully migrate to the metastatic tumor mass. As altered homing of tumor reactive immune cells is a potential target of melanoma immunotherapies, a growing number of revealed details about lymphocyte migration and its influencing circumstances is indispensable to successfully administered adoptive cancer therapy.

CTCL-cells in MF and SS alike are also guided to cutaneous tissues by the skin addressin CLA and certain chemokine receptors expressed on tumor cells. The number of circulating CLA+CTCL-cells was found to correlate with extension of skin lesions in SS, while serum levels of CTCL-attracting chemokines CCL17 and CCL27 were

demonstrated to correlate with disease severity both in MF and SS. Novel evidence suggests that MF and SS arise from distinct cell lines with different homing abilities and are probably therefore characterized by diverse clinical course and prognosis. Getting further insight into the molecular background of lymphoma cell homing is necessary as inhibition of CTCL-migration is expected to bring a new perspective to targeted therapy of CTCL forms.

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