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Cutaneous T-cell Lymphoma: Molecular Genetics, Immunology and Pathogenesis

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INTRODUCTION

NON-HODGKIN'S LYMPHOMAS (NHL) includes a group of neoplasms that share a common target tissue, i.e. lymphoid cells. This group is characterised by a high degree of biological and clinical heterogeneity. Besides the spleen and lymph nodes, NHL may develop in extranodal organs which may be related to physiological extranodal lymphocytic migration within the normal immune system. The primary localisations of NHL in the skin represents one of the most common localisation of extranodal NHL [1]. The majority of cutaneous lymphomas derive from T-cell lineage whereas most nodal NHLs derive from B-cell lineage. The term cutaneous T-cell lymphoma (CTCL) was first used by Lutzner and associates in 1975 and has become widely accepted [2]. Most cases of CTCL are characterised by a malignant proliferation of $CD4^+$ helper T lymphocytes [3, 4]. However, a few cases have been described in which the neoplastic cells express a suppressor/cytotoxic or $CD8^+$ T-cell phenotype [5]. The prototype of CTCL is the cerebriform T-cell lymphoma, which is historically subdivided into mycosis fungoides (MF) and Sezary syndrome (SS). MF typically presents as cutaneous patches that can progress to infiltrated plaques and ultimately cutaneous tumours with lymphoid and visceral involvement. In SS, there is involvement of blood, lymph nodes, spleen, liver and skin associated with erythroderma and typically sparing of bone marrow. The tumour cells show characteristic, cerebriform nuclei (Sezary cells) and have a predilection for involvement of epidermis, either individually or in clusters referred to as Pautrier microabscesses [6]. CTCL other than MF/SS represent a rather heterogeneous group of cutaneous lymphomas which differ in morphology, immunopathology and clinical course of the disease [7–10]. At present, there is no concensus on a definition and terminology of these lymphomas. Our present use of CTCL designation may include MF, SS, small to medium pleomorphic T-cell lymphoma, medium to large pleomorphic T-cell lymphoma $CD30^+$ large cell anaplastic lymphoma and T immunoblastic lymphoma (Table 1).

MOLECULAR GENETICS

Malignant cells in CTCL harbour an abnormal karyotype, either widely heteroploid or hyperdiploid or pseudoploid, with

Table 1. Classification of primary cutaneous T-cell lymphomas

Mycosis fungoides
Sezary syndrome
T-pleomorphic lymphoma, small to medium
T-anaplastic large cell lymphoma
T-pleomorphic lymphoma, medium to large
T-immunoblastic lymphoma

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various marker chromosomes [11–15]. Complex cytogenetic abnormalities are found more commonly on chromosomes 1 and 6, and may involve activation of oncogenes such as *ERB A, K-RAS, FPS* and *ICK*. In addition, abnormal expression of *C-MYC* has been detected [16–18]. However, no obvious cytogenetic abnormality or specific oncogene activation is consistently found in CTCL.

The main interest is focused on the problem of whether CTCL arises (i) from a single malignant clone of mature T-cells or (ii) from an immature stem cell clone that mature into independent and different T-cell clones, or (iii) originates simultaneously from independently transformed T-cells. Clonal T-cell populations in early phases of the disease would favour the first hypothesis whereas polyclonal T-cell infiltrations would exclude this pathway of neoplastic transformation. Clonality of T-cell proliferations generally is demonstrated by analysis of the rearrangement of the T-cell receptor (TCR) gene segments. This can be done by analysis of the rearranged V genes, e.g. by Southern blot analysis or by the polymerase chain reaction (PCR), or alternatively by staining with a monoclonal antibody specific for certain families of TCR variable regions. However, only four of a total of at least 20 Vβ-chain families can now be identified using monoclonal antibodies.

Amplification of rearranged TCR gene segments by PCR may be a possible means of sensitive detection of clonal T-cell populations in early skin lesions [19–21], as well as in the monitoring of disease progression involving peripheral blood and lymph nodes [22]. In advanced stages of the disease, clonality of the T-cell in CTCL has been demonstrated by analysis of the TCR rearrangement [23–26]. Clonal TCR-β gene rearrangements are frequently found in skin lesions of patients with advanced stages of the disease. However, Southern blot analyses have failed to detect discrete rearranged TCR gene segments at early stages of the disease. Using PCR techniques of 23 CTCL in early phases of the disease, Bignon and associates [27] reported five to be clonotypically heterogeneous with respect to the TCR-β and TCR-γ rearrangement when examining different tumour sites. This high frequency of clonotypic heterogeneity is more often observed in B-cell lymphomas and lymphoproliferative disorders than in T-cell lymphomas. The unexpected high frequency of clonal heterogeneity observed by Bignon and colleagues may be explained by the evolution of subclones with different multiple rearrangements from a single undifferentiated malignant cell with non-rearranged TCR. Alternatively, it cannot be excluded that two or more clones independently transformed to neoplastic cells. However, these observations were not confirmed by other groups [22, 28], who repeatedly found clonal rearrangements of TCR genes when analysing different sites of tumour involvement. Most interestingly, by means of V region-specific monoclonal antibodies, Jack and associates [29] demonstrated that the T-cells in 10 of 16 cases of MF and SS expressed a TCR-β with a variable region belonging to the Vβ8 gene family. All the positive cases were examples of the plaque or tumour stages of CTCL. This highly restricted Vβ8 gene usage is surprising since, based on the normal distribution of Vβ8-positive cells, only 3–5% of lymphomas were expected to react with the Vβ8-specific antibody. The unexpected frequent use of one particular V gene family suggests that CTCL might derive from a distinct subpopulation of T-cells, possibly selected by antigenic or viral stimulation. However, cell populations with restricted V gene usage are not necessarily monoclonal or malignant, but are generally taken as evidence for malignancy. Poppema and Hepperle [30] reported restricted V gene usage in 29% of TCR-positive lymphoblastic T-cell lymphomas analysed compared to 15% of normal peripheral T-cells that express these β-chain families. However, no preferential expression of V gene-specific families could be demonstrated. Interestingly, immunohistological staining of an early MF lesion with a Vβ8-specific monoclonal antibody demonstrated a strict intraepidermal localisation of the clonal T cells [31]. The epidermal part of the infiltrate is further characterised by the loss of CD5 expression in contrast to reactive infiltrating T-cells. A similar intraepidermal clone with Vβ8 expression in early MF has been reported by Boehnke and associates [32], whereas the dermal lymphocytes were Vβ8 negative, suggesting that the dermal part of the infiltrate is mainly composed of reactive lymphocytes.

CELLULAR IMMUNOLOGY

Immunophenotype

T-cell malignancies can be classified to corresponding stages of normal T-cell ontogeny by means of differentiation antigens. The immunophenotype of CTCL cells ($CD2^+CD3^+CD5^+$) indicates their mature post-thymic (peripheral) origin. In the majority of MF and SS cases, the T cells are of a mature $CD4^+CD45RO^+CD45RA^-$ "memory" T-cell phenotype. Occasional cases are reported to be $CD4^-CD8^+$ or $CD4^+CD8^+$ [33, 34]. The neoplastic cells generally express the TCR-α/β heterodimer, although rare cases expressing the γ/δ− TCR have also been described [35]. According to the degree of activation—indicated by the expression of activation-associated antigens such as CD25 and CD30 antigens—CTCL can be divided into several groups: MF and SS express no or only a few of the activation antigens, pleomorphic T-cell lymphoma consist of mixtures of activated and non-activated cells whereas T-immunoblastic and anaplastic large cell lymphoma are composed of an almost homogeneous population of activated T-cells [34, 36–38].

Aberrant surface antigen expression is often seen in CTCL, particularly in advanced plaque or tumour stage lesions [34, 39–41]. This includes diminished or absent expression of pan T-cell antigens (CD2, CD3) or absent T-cell subset antigen expression (CD4, CD8). However, the distinction between early MF or SS lesions and histologically similar benign dermatoses, e.g. chronic eczema, has not been facilitated by the use of even extensive panels of monoclonal antibodies. The studies have shown that most of the T-cells in normal skin and benign dermatoses express the $CD4^+CD45R^+CD45RA^-$ "memory" phenotype. Thus, tumour cells in the early phase of MF and SS are phenotypically indistinguishable from mature T-cells, with the exception of CD7 expression. CD7 is one of the major T-cell

Table 2. Predominant immunophenotype of circulating tumour cells in peripheral T-cell lymphomas

Antigen	T-PLL	T-CLL	ATL/L	Sezary syndrome/MF
CD3	+	+	+	+
CD4	+	+	+	+
CD8	−	−	−	−
CD7	+	+/−	−	−
CD25	−	−	+	−
CLA	−	−	−	+

T-PLL, prolymphocytic leukaemia; T-CLL, chronic lymphocytic leukaemia; ATL/L, adult T-cell lymphoma/leukaemia; MF, mycosis fungoides; CLA, cutaneous lymphocyte antigen.

antigens expressed very early during T-cell ontogeny [42], and therefore, represents a useful clinical marker for the diagnosis of T-cell malignancies [43, 44]. Sezary cells generally lack CD7 expression, and cutaneous infiltrates in CTCL lesions have been found to contain a high number of CD7-negative T-cells [4, 45]. Several authors have suggested that absent CD7 expression in CTCL is the result of antigen loss (aberrant phenotype) and, therefore, may be helpful in differentiating malignant lymphoma from reactive benign infiltrates in early MF lesions [46]. However, several results indicate that lack of CD7 expression is not restricted to malignant T-cells, but is also found in benign inflammatory skin lesions, as well as in the majority of epidermal and dermal T-cells of normal skin [47–51].

Recently, we characterised a subpopulation of $CD7^-$ T-cells in the peripheral blood of normal donors [52, 53]. Northern blot analysis revealed absence of CD7 expression at the mRNA level. The majority of circulating $CD7^-$ T-cells in healthy donors are of the $CD4^+$ "memory" phenotype. Our recent results showed that this subpopulation represents a separate lineage of late T-cell differentiation (U Reinhold, University of Bonn, Germany, personal communication). These data indicate that absence of CD7 in CTCL is not due to antigen loss but represents an expansion of a cell population not expressing the antigen. Labastide and colleagues [54] recognised a surface antigen (CH-F42) which is expressed on circulating Sezary cells and adult T-cell lymphoma leukaemia but which is negative in a variety of other haematological malignancies. Interestingly, CH-F42 is also expressed on normal circulating $CD7^-$ T-cells. Studies from Picker and associates have shown that the majority of T-cells infiltrating cutaneous sites of inflammation express the cutaneous lymphocyte antigen (CLA) carbohydrate ligand for ELAM-1 (endothelial lymphocyte adhesion molecule 1), which appears to act as a skin lymphocyte homing receptor [55–57]. CLA is expressed in a high number of CTCL, but is absent from most nodal T-cell lymphoma. Picker and colleagues [58] showed that CLA is also expressed on a subset of normal circulating $CD4^+$ helper cells. We have further demonstrated that a high number of normal circulating $CD7^-$ T-cells express CLA antigens [50]. Immunoelectronmicroscopic studies performed by Matutes and associates [59] revealed that normal circulating $CD4^+CD8^-CD7^-$ T-cells may exhibit a cerebriform nuclear pattern characteristic of Sezary cells. Alternatively, it has been shown that the distinctive convoluted nuclear morphology of Sezary cells is not restricted to a distinct subset of T-cells. Sezary-like morphology can be induced *in vitro* in a number of normal T-cells by activation via the T-cell receptor/CD3 complex and CD2 antigens, which suggests that there is no obligatory morphological association between the malignant Sezary cell and its possible physiological counterpart [60, 61]. Based on these observations, we support the concept that dermatotropic T-cells contribute a unique tissue-restricted subpopulation of normal human T-cells which may represent the counterpart of CTCL. The present results indicate that a distinctive subset of post-thymic mature helper T cells defined by the expression of CLA and consecutive absence of CD7 antigen expression may be a candidate counterpart for certain forms of CTCL.

Functional studies

Functional studies of tumour cells in CTCL are limited due to the fact that these cells respond poorly to conventional cell mitogens and T-cell growth factors [62–65]. However, malignant Sezary cells purified from peripheral blood were shown to provide profound help in a pokeweed mitogen-driven co-culture system with normal B cells, which indicates that these cells correspond to those of functional active mature helper T-cells [66, 67]. In correlation, clinical observations of the associated hypergammaglobulinaemia, often with specific increases in the serum IgA and IgE levels, suggest that the augmentation and amplification of immunoglobulin synthesis by normal B cells is a function retained by these neoplastic cells.

In contrast to other investigators, certain groups have been successful in establishing long-term T-cell lines from patients with CTCL [68–70]. The majority of these cell lines were generated from the peripheral blood of patients with SS. Abrams and colleagues [69] established malignant T-cell lines in a high percentage by using a combination of conditioned medium containing interleukin-2 (IL-2) and a yet undefined "Sezary T-cell activating factor" derived from mitogen-stimulated peripheral blood mononuclear cells (PBMC) from one selective Sezary patient. In agreement with other groups, we observed that incubation of cells derived from CTCL skin lesions in the presence of IL-2, with or without T-cell-activating agents, selectively propagates polyclonal, presumably non-malignant T-cells [71–73]. These cells correspond to the polymorphous infiltrate comprised of malignant T-cells, but also normal-appearing lymphocytes usually observed in histological sections of CTCL skin lesions. Immunological studies at the clonal level showed that the phenotypes and functional profiles of tumour-infiltrating lymphocytes (TIL) in CTCL are rather heterogenous. Although TIL in CTCL may exert cytotoxic activity against autologous lymphoma cells *in vitro*, it remains to be determined whether TIL can be used in adoptive immunotherapy. In a case of advanced MF, we clearly demonstrated that TIL may also contain T-cells which can profoundly downregulate immune responses and, therefore, may lead to suppression of antitumour immunity *in vivo* [71].

Recent results have shown that CTCL cells express IL-7 receptor (IL-7-R) mRNA and that exposure of these cells to IL-7 *in vitro* further increases IL-7-R expression as well as IL-2-R expression [74]. Furthermore, IL-7 can induce proliferation in CTCL cells and may mediate synergistic stimulation in combination with IL-2 [74, 75]. Further indication for a possible pathophysiological role of IL-7 in CTCL has been provided by Rich and colleagues [76], showing that IL-7 transgenic mice develop cutaneous lymphoma. These lymphomas are of T-cell origin and secrete and respond to IL-7. The data implicate that IL-7-R antagonists may be of interest for the development of novel therapeutic strategies in certain forms of CTCL.

CYTOKINES

Immunological features of patients with CTCL include increased levels of IgE and IgA, eosiniphilia and decreased IL-2-R expression [77–79]. Over the last years, it has become evident that soluble factors, such as lymphokines, derived from helper T-cells, may play a significant role in the pathogenesis of these abnormalities [80]. For example, human IgE synthesis is regulated by different T-cell-derived cytokines, including IL-4 and IFN-γ [81]. These factors have been shown to play reciprocal roles in the regulation of IgE responses *in vitro* and *in vivo*: IL-4 promotes and IFN-γ inhibits its production. IL-5 has been shown to exert growth-promoting properties for eosinophils [82]. Mosman and colleagues [83] demonstrated that murine helper T-cells are composed of at least two non-overlapping subsets that can be distinguished on the basis of their patterns of cytokine secretion. One subset (Th_1) produces IL-2 and IFN-γ whereas the other T-cell subset (Th_2) secretes IL-4 and IL-5,

but does not secrete IL-2 and IFN-γ. In humans, the majority of normal helper T-cell clones exhibited a mixed pattern of cytokine secretion, but Th_1 and Th_2 clones have been described and seem to play a significant role in certain pathological conditions, e.g. allergic diseases [84, 85]. Based on these results, research has focused on the cytokine secretion pattern of malignant T-cells in CTCL. In fact, results from Dummer and associates [86] demonstrated that PBMC in CTCL patients produce increased amounts of IL-4 and IL-5 and are defective in producing IL-2 and IFN-γ. Vowels and colleagues [87, 88] found that tumour cells in CTCL may secrete Th_2-related cytokines and may constitutively express mRNA for IL-4 and IL-5. Thus, there is strong evidence that in certain forms of CTCL, the malignant clone may exert Th_2-like activities via IL-4 and IL-5, which may help explain the observed immunological abnormalities found in these patients. Furthermore, the present results have implications for the development of novel treatment strategies for CTCL patients by altering the balance between Th_1 and Th_2 activities. These approaches might include *in vivo* application of cytokines such as IFN-γ, which has been shown to exert significant Th_2-antagonistic effects *in vitro* and *in vivo* [89, 90]. Results from a first clinical study with recombinant IFN-γ in CTCL revealed therapeutic benefit at least in a subgroup of patients [91].

EPIDERMOTROPISM

One of the major characteristics of malignant T-cells in CTCL is their marked affinity for the skin termed epidermotropism. At present it is unknown why the malignant lymphocytes localise to the skin. One possible explanation for epidermotropism may include intrinsic properties inherent in the specific T-cell population. Adhesion molecule interactions are supposed to play a cardinal role in cell–cell and cell–matrix interactions. Thus, extravasation of organotropic T-cells to the skin may be dependent on the interaction between CLA with E-selectin, which has been shown to be preferentially induced on cutaneous venuoles [55]. Savoia and associates [92] found that skin-infiltrating Sezary cells show a unique expression of one subtype of integrins ($\alpha 3\ \beta 1$). The integrin $\alpha 3\ \beta 1$ binds to laminin, fibronectin, and collagen types I and IV, and the affinity of Sezary cells to the skin has been related to its expression. Other data indicate that specific signals derived from the skin may be relevant for epidermotropism in CTCL. Patients with MF and SS show intense epidermal lesional levels of IL-1, IL-6 and IL-8 compared to normal skin and skin lesions of benign inflammatory dermatoses [93–96]. IL-8 is a potent chemoattractant for T-cells and, thus, may attract skin-infiltrating lymphocytes to the epidermis. However, it is unclear whether these cytokine abnormalities found in CTCL skin lesions precede the arrival of T-cells or whether skin-infiltrating T-cells subsequently upregulate the epidermal production and release of certain cytokines.

AETIOLOGY

The aetiology of CTCL is poorly understood, but genetic factors, environmental factors and infectious agents have been suggested as possibly relevant factors. Rare cases of CTCL within families, including MF in siblings, have been reported [97–99]. In addition, increased frequency of major histocompatibility complex (MHC) antigens AW3, AW32, B8, BW35 and DR5 have been observed [100, 101]. Other investigators found an increased incidence of CTCL in people employed in a manufacturing occupation, particularly in association with exposure to petrochemicals, metals, pesticides or herbicides [102, 103]. However, case–control studies could not confirm these findings [104, 105]. Other groups suggest a retroviral aetiology for CTCL. This, until recently, controversial hypothesis has been initiated due to the finding that a significant percentage of CTCL patients showed serum antibodies reactive with human T-cell lymphotropic virus type I (HTLV-1) proteins [106]. Furthermore, Hall and colleagues [107] found deleted HTLV-provirus in cutaneous lesions of MF patients, and other groups confirmed these results by detecting deleted HTLV-I proviral DNA in CTCL patients [108–110]. Zucker-Franklin and colleagues [70] demonstrated HTLV-like particles in cultured lymphocytes of 18 of 20 patients with MF. Furthermore, they found HTLV-I pol-specific sequences in 4 of 9 patients, and HTLV-II pol-specific sequences in 1 patient. These results are in contrast with those of other investigators who failed to detect HTLV-I serum antibodies or HTLV-I sequences in the peripheral blood or skin of CTCL patients [111, 112]. Thus, the role of retroviruses in the aetiology of CTCL remains uncertain. A possible explanation for the conflicting results may be that retrovirus infection is associated only with certain subtypes of CTCL, or may be related to the geographical origin of the patients. Other groups suggest that Epstein–Barr virus (EBV) infection may play a role in the aetiopathogenesis of CTCL. Lee and associates [113] found serum antibodies against EBV nuclear antigens in all 21 patients with CTCL studied. Jones and colleagues [114] identified EBV in 3 cases of fatal $CD4^+$ T-cell lymphoma, 2 of whom had skin involvement. Furthermore, several cases of CTCL in association with human immunodeficiency virus (HIV) infection have been reported [115, 116]. The clinical and immunopathological spectrum appears diverse. Many cases of CTCL in the acquired immunodeficiency syndrome (AIDS) show an aggressive course and may express the $CD8^+$ phenotype. However, Burns and associates [117] described two HIV-1-seropositive, HTLV-1-negative patients with typical, slowly progressive course of MF without history of AIDS. In conclusion, several different factors may be involved in the aetiology of CTCL, which have to be evaluated in future research.

CONCLUSIONS

Cerebriform mononuclear cells are the morphological hallmark of certain CTCL, including MF and SS. Although the irregular nuclear contour of the tumour cells is characteristic of these T-cell lymphomas, recent results demonstrated that cerebriform nuclear morphology is associated with cell activation via the T-cell receptor/CD3 complex and CD2 antigens in normal human T-cells, emphasising the non-specificity of this phenomenon. Immunophenotyping has shown CTCL to be a malignant proliferation of mature $CD4^+CD8^-$ helper T-cells, in which the circulating malignant cells characteristically lack CD7 antigen expression. Absent CD7 antigen expression on CTCL cells seems to reflect an expansion of a T-cell subpopulation not expressing the antigen rather than a true aberrant immunophenotype. $CD7^-$ T-cells represent a subset of post-thymic helper T-cells in the peripheral blood of normal individuals and have been shown to accumulate in certain benign inflammatory skin lesions. The present results indicate that a subset of normal human $CD7^-$ T-cells may represent the physiological counterpart of certain forms of CTCL. Functional and molecular characterisation of physiological populations of skin-restricted T-cell subsets and their possible relation to malignant cells in CTCL is justified. These studies may further advance our

understanding of CTCL pathogenesis and form a strategic basis for therapeutic interventions.

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Conformal Radiation Treatment: a Critical Appraisal

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INTRODUCTION

IN THE last decade, advances in engineering and computer science have facilitated the implementation of high precision and high dose radiation treatment, the so-called 3-dimensional conformal radiotherapy (3DCRT). The advanced technology includes high-speed graphics workstations [1, 2], multileaf collimators [3, 4], computer-controlled treatment machines [5] and on-line portal imagers [6]. In conjunction, approaches and