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Review article

Molecular pathogenesis of Cutaneous T cell Lymphoma: Role of chemokines, cytokines, and dysregulated signaling pathways

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ABSTRACT

Cutaneous T cell lymphomas (CTCLs) are a heterogeneous group of lymphoproliferative neoplasms that exhibit a wide spectrum of immune-phenotypical, clinical, and histopathological features. The biology of CTCL is complex and remains elusive. In recent years, the application of next-generation sequencing (NGS) has evolved our understanding of the pathogenetic mechanisms, including genetic aberrations and epigenetic abnormalities that shape the mutational landscape of CTCL and represent one of the important pro-tumorigenic principles in CTCL initiation and progression. Still, identification of the major pathophysiological pathways including genetic and epigenetic components that mediate malignant clonal T cell expansion has not been achieved. This is of prime importance given the role of malignant T cell clones in fostering T helper 2 (Th2)-bias tumor microenvironment and fueling progressive immune dysregulation and tumor cell growth in CTCL patients, manifested by the secretion of Th2-associated cytokines and chemokines. Alterations in malignant cytokine and chemokine expression patterns orchestrate the inflammatory milieu and influence the migration dynamics of malignant clonal T cells. Here, we highlight recent insights about the molecular mechanisms of CTCL pathogenesis, emphasizing the role of cytokines, chemokines, and associated downstream signaling networks in driving immune defects, malignant transformation, and disease progression. In-depth characterization of the CTCL immunophenotype and tumoral microenvironment offers a facile opportunity to expand the therapeutic armamentarium of CTCL, an intractable malignant skin disease with poor prognosis and in dire need of curative treatment approaches.

1. Introduction

Cutaneous T cell lymphomas (CTCLs) represent a broad, highly heterogeneous grouping of lymphoproliferative disorders characterized by the neoplastic development of clonally-derived malignant skin-homing or skin-resident memory T lymphocytes. It is a relatively uncommon skin disease, although increasing incidence rates have been reported in the past three decades with approximately 3,000 new cases registered per year in the United States [1] and 350 new cases in the United Kingdom [2]. Epidemiologic studies have documented geographic clustering as well as demographic (age, race, sex) trends of CTCL cases [3]. Known to primarily affect males [1] and Caucasian individuals over 55 years old, new demographic data has reported younger age presentation and an aggressive clinical course in African-American, Hispanic, and Middle-Eastern individuals [3–6].

In terms of clinical behavior and prognosis, CTCLs are recognizably distinct from the histologically similar systemic lymphomas and their associated secondary cutaneous presentations [7]. However, their

Abbreviations: CTCL, Cutaneous T cell lymphoma; MF, Mycosis fungoides; SS, Sézary syndrome; TME, Tumor microenvironment; IL, Interleukin; Th1, T helper 1; Th2T, helper 2; TIL, Tumor-infiltrating lymphocyte; DC, Dendritic cell; KC, Keratinocyte; TLR, Toll-like receptor; TCR, T cell receptor.

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Table 1
Classification of CTCL variants with their clinical and histologic features.

CTCL entities	Clinical presentation	Histopathologic work-up	References
Classical Mycosis Fungoides (MF)	Pink or erythematous scaly patches and infiltrated plaques	• Epidermotropic infiltrate of lymphocytes • Pautrier's microabscesses-intraepidermal clusters of atypical lymphocytes • Large cell transformation (advanced stages)	[126,242]
MF variants			
Folliculotropic MF(FMF)	Acneiform lesions, follicular papules or alopecic plaques formation on the scalp, face, neck, and upper trunk	• Dense lymphocytic infiltrates into the hair follicle epithelia	[126,243]
Granulomatous slack skin	Bulky skin folds seen in the intertriginous folds	• Granulomatous T cell infiltrates • Loss of elastic fibers	[126,244]
Pagetoid reticulosis (PR)	Psoriasiform lesion seen on acral sites	Prominent epidermotropic lymphocytic infiltrate	[126]
Sézary syndrome (SS)	Erythroderma, generalized lymphadenopathy, pruritus	• Single lymphocyte epidermotropism, • Telangiectasias • Slight dermal infiltrate	[126,245]
Adult T cell leukemia/ lymphoma (ATL/ATLL)	Nodulotumoral, plaques, multipapular, patches, erythrodermic and purpuric skin eruptions	• Epidermotropism • Pautrier microabscess	[246,247]
Primary cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPD)			
Lymphomatoid papulosis (LYP)	Grouped or disseminated papules and small nodules	• Dermal lymphocytic infiltrate • Medium to large-sized lymphoid cells (with nuclear pleomorphism) admixed eosino-phils and histiocyte	[248]
Primary cutaneous anaplastic large cell lymphoma (PC-ALCL)	Rapidly growing large ulcerated tumors.	Infiltrates of large pleomorphic or anaplastic tumor cells	[126]

(*continued on next page*)

Table 1 (*continued*)

CTCL entities	Clinical presentation	Histopathologic work-up	References
Subcutaneous panniculitis-like T cell lymphoma (SPTCL)	Subcutaneous plaques or nodules, focal lipoatrophy	• Lobular panniculitis • Lymphocyte and macrophage-containing infiltrate	[126,249]
Primary cutaneous peripheral T-cell lymphoma, rare subtypes			
Primary cutaneous γ/δ T cell lymphoma (CGD-TCL)	Formation of necrotic and ulcerated plaques, nodules, and tumors	Epidermotropic and subcutaneous infiltrates	[126]
Primary cutaneous aggressive epidermotropic CD8-positive T cell Lymphoma (CD8+ AE-CTCL)	Necrotic or ulcerated plaques and tumors	• Epidermal ulceration, • Pandermal and epidermotropic lymphocytic infiltrate	[242,250]
Primary cutaneous CD4+ small/medium-sized pleomorphic T cell lymphoproliferative disorder (CD4+SMT-LPD)	Papule or nodule on the face, neck, or upper trunk	Dense, nodular, and diffuse or superficial lymphoid infiltrate	[251]
Primary cutaneous acral CD8+ T cell lymphoma (CD8+ ATCL)	Slow-growing nodule, without patches or plaques	Proliferation of monomorphic, intermediate-sized CD8+ T cells	[252]
Extranodal NK/T cell lymphoma, nasal type	Nasal obstruction, epistaxis, facial swelling, lethal midline granuloma	Polymorphic infiltrate of lymphoma cells and non-neoplastic inflammatory cells	[253]

Table 2
Cytokines in CTCL pathogenesis.

Cytokines	Profile	Signaling pathways	Regulatory role/function in CTCL	References
IL-2	Th1	JAK/STAT PI3K/mTOR MAPK/ERK	• Stimulates proliferation and survival of malignant T cells • Generates inducible FoxP3+ Treg cells via STAT5 • Immune evasion	[36,254]
IL-4	Th2	JAK/STAT	• Promotes tumor cell proliferation • Stimulates Th2 predominance and immune defects • Induces secretion of Th1 chemokines	[16,70]
IFN-γ	Th1	JAK/STAT	• Decreased expression in advanced stages associated with immune suppression and skewing towards Th2 inflammatory TME	[60,109]
IL-8	P Pro-inflammatory	NF-κB	• Involved in non-histaminergic itch • Promotes neutrophil chemotaxis • Impairs differentiation of infiltrated monocytes into mature DCs	[98,255]
IL-10	Th2	NF-κB	• Abrogates Th1 responses • Immune suppression • Promotes M2 polarization of TAMs • Promotes tumor growth	[72,73,208]
IL-12	Th1	JAK/STAT (STAT4)	• Induces IFN-γ production • Activates cytotoxic lymphocytes • Decreased expression associated with stage-related defects in cell-mediated immunity and in Th1 cytokine production	[103,163,164]
IL-13	Th2	STAT6	• Impairs antibacterial protein induction causing cutaneous bacterial infections • Promotes Th2 phenotype in CTCL cells and non-malignant T cells • Promotes malignant transformation of T cells	[60,256]
IL-15	Pro- inflammatory	STAT3	• Induces FoxP3 expression • Immune evasion	[36,81]
IL-17A	Pro- inflammatory	STAT3	Drives angiogenesis • Facilitates CTCL cell metastasis via IL-22/CCL20/CCR6 axis	[257]
IL-22	Pro- inflammatory	STAT3	• Induces epidermal hyperplasia through STAT3/CCL20 axis • Plays crucial role in disease development	[61,257]
IL-31	Th2	JAK1/2-STAT RAS/ERK PI3K/Akt MAPK	Involved in advanced CTCL-associated non-histaminergic itch • Autocrine growth factor in CTCL	[98,258]
IL-32	Pro- inflammatory	NF-κB	• Promotes cell proliferation and viability • Upregulates survival genes	[74,76]

classification remains ambiguous and ill-defined but is constantly updated. Currently, the classification and terminology are based on the revised WHO 2017 classification and the updated 2018 World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) consensus classification for skin tumors monograph [8,9]. The majority of CTCL cases are comprised of mycosis fungoides (MF), accounting for approximately 60 % of CTCL cases, and CD30+ lymphoproliferative disorder (LPD), accounting for approximately 25 % of CTCL cases. Rare distinct CTCLs have also been defined, such as Sézary syndrome (SS), constituting around 5% of CTCL cases. The rarest subtypes, representing up to 2% of the cases, include entities with an indolent clinical course and limited distribution, such as primary cutaneous CD4+ small/medium T cell LPD (SMPTC-LPD), primary cutaneous acral CD8+ T cell lymphoma (acral CD8+ TCL) and subcutaneous panniculitis-like TCL (SPTCL) as well as those with an aggressive course, such as primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma (CD8+ PCAETL) or primary cutaneous γδ T cell lymphoma (PCGDTCL) [7,10–12] (Table 1). In comparison to the well-characterized spectrum of MF/SS and LPD, the exact characterization and classification of other rare CTCL variants is controversial and incomplete. This diagnostic inaccuracy at the molecular level, together with their rare occurrence and clinicopathologic overlap, has resulted in limited therapeutic approaches and a lack of treatment recommendations [13]. As MF and SS are well-researched amongst all CTCL entities and collectively account for the majority of cases, our review will primarily focus on these 2 clinical variants addressed hereafter by the term 'CTCL' unless specified otherwise.

CTCL encompasses a wide range of clinical, histological, molecular, and immunophenotypic features. Clinicopathologically, the most well-defined CTCL entity is MF, which exhibits broad clinical presentations ranging from localized cutaneous single lesions (flat erythematous patches in photo-protected areas) to more generalized distribution (erythroderma) and nodules with orwithout ulceration [14]. MF shows characteristic disease evolution, typically evolving through progressive stages IA-IVB [15]. In the early stages, MF has indolent clinical behavior and is typified by pruritic erythemato-squamous plaques with benign inflammatory features that resemble chronic eczemas, allergic contact dermatitis, psoriasis, and large-plaque parapsoriasis [16]. Such inflammation-simulating clinical features account for the substantial diagnostic delay in early-stage MF cohorts. The great clinical variability of MF lesions (e.g. hypopigmented, verrucous, etc.), the lack of singular diagnostic test, and undefined prognostic indices further add to the difficulty [17]. Over the period of years, even decades, the lesions may progress into infiltrated plaques (plaque stage) or large intradermal ulcerated tumors (tumoral stage) composed of cytomorphologic, phenotypic, and genotypic abnormal tumor cells. In a subset (30 %) of patients [18], the disease can progress aggressively and eventuate in erythroderma (confluent erythematous, pruritic patches/plaques covering at least 80 % of total body surface area) or extracutaneous involvement, preferentially to lymph node/peripheral blood [15]. Overt leukemic or organ involvement is typically associated with a poor prognosis arising from both malignant invasion and immunosuppression.

Sézary syndrome is an aggressive leukemic CTCL entity that is clinically characterized by the triad of erythroderma (with severe intractable pruritus/itch), enlarged lymph nodes, and the distribution/accumulation of clonal atypical cerebriform T cells in the skin, peripheral blood (so called Sézary cells), and lymph nodes [7,19]. Clinically, SS may occur *de novo* or evolve gradually in patients with chronic MF [20]. SS is considered a late stage of CTCL because of its aggressive nature [8,16,21,22]. It typically presents a grim prognosis that is heavily influenced by systemic problems and comorbidities, such as cardiovascular diseases in older patients, hypoproteinemia, compromised temperature regulation, and increased predisposition to opportunistic infections and sepsis; the latter being frequently associated with high mortality in SS patients [23].

Given the strikingly similar morphologic and phenotypic features, SS

and MF seem to be closely related. Recent high-definition transcriptomic studies employing next generation sequencing (NGS) technologies have established a comprehensive overview of the genomic and epigenetic landscape of CTCL and uncovered the complex mutational spectrum of MF and SS, with a strong link to their occurrence and progression. Functionally, this has led to the identification of >50 driver mutations [24] (with a strong bias for somatic copy number variants (SCNVs) compared to somatic mutations) [25] and common mutagenic pathways that essentially 'drive' CTCL pathogenesis. MF/SS variants typically exhibit somatic mutations, amplifications, or deletions in genes that participate in key cellular processes, including immune-synapse signaling [25], DNA damage response [25], programmed cell death [26], and cell-cycle regulation [27]. Mutational changes in various signaling cascades such as T cell receptor (TCR), nuclear factor-kappa B (NF-κB) [26,28] and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) [29] pathways that are highly relevant to CTCL pathogenesis have also been uncovered. Moreover, numerous studies have reported the accumulation of epigenetic alterations, including changes in chromatin accessibility and DNA methylation profile, histone modifications, and microRNA (miR/miRNA) regulation, which in turn contribute to malignant transformation and disease progression in MF/SS [30–32]. Regardless, the identification of the major cancer drivers or the collection of genetic and epigenetic events that underscore the expansion of malignant clonal T cells has not been achieved.

For decades, CTCL has been traditionally described as a monoclonal disease arising from the expansion of mature memory CD4+ helper T cells. Challenging this view, Campbell et al. [33] identified MF and SS as biologically distinct lymphomas that originate from distinct functional T cell subsets. According to the observations, SS cells are derived from central memory T (T_{CM}) cells, whereas MF cells are derived from effector memory T (T_{EM}) cells. This concept has been widely accepted as the most plausible explanation for the different clinical behaviors of these 2 subtypes that otherwise show overlapping cytologic and immunophenotypic features. Nevertheless, advances in single-cell sequencing technology, including droplet-based single-cell RNA-sequencing (scRNA-seq) have questioned this dogma by presenting an unprecedented view of lymphocyte heterogeneity and revealing substantial inter- and intra-patient phenotypic heterogeneity and phenotypic plasticity [34–36]. In fact, CTCLs represent a paradigm for the heterogeneity and dynamic complexity of neoplastic disorders. Several studies have demonstrated at least some level of heterogeneity in the malignant cell population, derived from each patient, which is manifested through the formation of complex aberrant clonal hierarchies and subclones. Supporting this notion, recent data has highlighted extensive single-cell heterogeneity in SS patient-derived primary malignant T cells and identified several distinct subpopulations among original clonal T cells that exhibit heterogeneous expression of surface markers characteristic of T_{EM}, T_{CM}, stem cell memory (T_{SCM}), naïve (T_N), or transitional memory (T_{TM}) T cell phenotypes [35,37,38]. Emerging evidence has also confirmed phenotypic shifts among major naïve/memory T cell subsets in both MF and SS, suggesting its importance as a functional state indicator rather than a cell-of-origin surrogate for SS and MF classification [39]. It has been suggested that the true functional heterogeneity of the lymphocytes in MF and SS reflects their phenotypic plasticity. One of the arguments supporting this phenomenon has been the demonstration of the cytokine-dependent transition of malignant T cells into immunomodulating regulatory T cells (Treg) and IL-17-producing helper T (Th17) cells during advanced stages of CTCL [36].

Recent developments focused on re-evaluating traditional perspectives on monoclonality and mature T cell origins of MF have been driven by the discovery of clonal heterogeneity, testifying to the possible origin of MF from immature early precursor T cells. MF has been shown to harbor different clonotypic compositions even in its early stages, with evidence on both inter- (topologic) and intra-lesional clonotypic diversity [40]. Extensive experimental findings by Hamrouni et al. [41] have identified the complex, polygonal nature of MF arising from substantial clonal heterogeneity and diversity with respect to TCR (TCRα, γ, and β sequence) gene rearrangements, corroborating with the immature precursor origin of MF. This heterogeneity/variation in clonotypic richness is speculated to be caused by a mechanism similar to that of consecutive tumor seeding. According to the model, the accrual of diverse neoplastic T cell subclones from the peripheral blood to the developing lesions of lymphoma leads to the transfer of diversity and the emergence of new genetically different subclones that are capable of reentering the circulation and seeding other skin lesions [40]. The diverse TCR clonality patterns favor the speculation of clinically distinctive but genetically linked neoplasms (such as MF and lymphomatoid papulosis) in the same patient and the concomitant involvement of multiple skin regions by new or relapsing MF [41]. Such intra-individual subclonal heterogeneity in TCR gene rearrangements has also been reported in SS patients. Using cell culture and patient-derived xenograft models, this clonal selection was found to be associated with immunophenotypic plasticity and limited genomic evolution [42]. Besides evidence of malignant clonality, previous studies have also identified oligoclonal or monoclonal populations of non-malignant skin-infiltrating lymphocytes in MF skin lesions that exhibit TCR gene rearrangements [16].

In addition to the phenotypic and clonal diversity, evidence of genomic heterogeneity has also been provided. Based on the current data, both MF and SS exhibit subclonal distribution of genomic aberrations (single-nucleotide variants (SNVs) and somatic copy-number aberrations (CNAs)). This subclonal enrichment of mutations accounts for extensive intratumoral heterogeneity (ITH), showing a branched phylogenetic relationship pattern. Notably, ITH has been credited for the divergent evolution of MF, in which each lesion, or rather individual T cell clone, evolves by accumulating mutations independently of one another [24]. Single-cell transcriptome profiling has also highlighted vast inter- and intra-tumor cell transcriptional heterogeneity, particularly in the T lymphocyte subset, in advanced CTCL skin samples [43]. Analysis of tumor-specific lymphocyte clusters have revealed unique transcriptional pattern of each cluster that are characterized by the expression of genes such as retinol dehydrogenase 10 (RDH10), C-X-C Motif Chemokine Ligand (CXCL) 13, secretogranin II (SCG2; CTCL-2), FGR proto-oncogene, Src family tyrosine kinase, insulin like growth factor binding protein (IGFBP) 2/6, neurofilament medium chain (NEFM; CTCL-5), anoctamin 1 (ANO1), transition protein 1 (TNP1), carboxylesterase 4 (CES4A), Zinc finger, DHHC-type containing 14 (ZDHHC14; CTCL-6), lectin, galactoside-binding, soluble, 7 (LGALS7), serpin peptidase inhibitor, clade B (SERPINB) 3/4, SPR2A (CTCL-8), neurotrophic receptor tyrosine kinase (NTRK2), and transmembrane protease serine 3 (TMPRSS3; CTCL-12) [43]. Such a complex genomic landscape of CD8+, CD4+, and Treg tumor-infiltrating lymphocytes (TILs) as well as variable expression of effector molecules and checkpoint receptor inhibitors has been associated with impaired antitumor response dominantly observed in CTCL patients.

Despite all of the evidence for CTCL heterogeneity, significant changes in the tumor inflammatory microenvironment are consistently observed as the disease progresses from early indolent to advanced metastasizing and symptomatic (recalcitrant pruritus) stages. These changes do not occur as an epiphenomenon; instead, they appear as critical checkpoints in disease progression. Accumulating evidence has asserted an increasingly important role of malignant T cells in fostering the inflammatory milieu and fueling progressive immune dysregulation and tumor cell growth in CTCL patients, manifested through the secretion of Th2 cytokines and chemokines. Herein, we summarize the inflammatory changes that accompany disease evolution and define the roles of cytokines, chemokines, and multiple signaling networks in driving immune defects, malignant transformation, and disease progression in CTCL.

2. Immune defects in CTCL: Th2-biased tumor microenvironment

The clinical and histological features of early lesional skin in CTCL bear a resemblance to benign inflammatory disorders due to the presence of dense benign immune cell infiltrates, with only a small share occupied by malignant T cells [44,45]. These benign cell infiltrates are primarily composed of reactive T helper 1 (Th1) cells and interferon (IFN)-γ-secreting CD8+ TILs [16,46]. Studies have established the cytotoxicity of these non-neoplastic mononuclear cells, manifesting a Th1-biased cytokine profile, against autologous tumor cells [47,48] as well as correlated their high numbers with improved survival in CTCL patients [46,49,50]. This suggests that an early disease stage represents an equilibrium phase whereby a vigorous cell-mediated antitumor immune response can actively abrogate the expansion of the malignant population [17].

Advanced stages, on the other hand, present several immunologic abnormalities including, defects in Th1 cytokine production (e.g. IFN-γ and interleukin (IL)-2) and a decline in the number of non-malignant immune cells [16,46] concomitant with markedly elevated expression of Th2 lineage-specific transcription factors (e.g. GATA-3) and cytokines (e.g. IL-4, IL-5, IL-13, and IL-31) [44]. In particular, with the increasing burden of circulating malignant T cells during disease progression, there is a drop in the number and activity of infiltrating CD8+ T cells, Th1 cells, and natural killer (NK) cells [16,51]. Such defects in cellular cytotoxicity caused by the Th2-dominated inflammatory tumor microenvironment (TME) have been found to profoundly affect both host antitumor immune response and immunity against microbial pathogens [52,53]. A better understanding of the mechanisms that contribute to this Th1-Th2 shift is essential to facilitate the development of therapies targeting the Th2 phenotype and state of immune evasion for improving both the anticancer and the anti-pathogen response in CTCL patients.

2.1. Role of cytokines in immune dysfunction and disease progression in CTCL

The two most common clinical entities of CTCL - MF or SS have a strong bias towards a Th2 phenotype, fostered by the functional polarization of cytokines towards a Th2 profile and the establishment of a Th2-dominant TME [54–56]. This cytokine-mediated shift from a Th1 to a Th2-dominated microenvironment has been shown to occur directly via repression of benign T cell responses or indirectly via modulation of chemokine expression patterns in the TME [57–59] (Table 2). Guenova et al. [60] demonstrated the capacity of Th2 cytokines, secreted by malignant T cells, to suppress benign Th1 responses in the leukemic variant of CTCL (L-CTCL). L-CTCL is a uniform malignancy of FOXP3+ Treg cells, Th17 cells [61–63], and Th2 cells [64–66]. However, its clinical presentation indicates the presence of Th2-driven immunologic response that is characterized by reduced Th1 responses, eosinophilia, and an increased level of serum immunoglobulin (Ig) E and A [67–69]. Supporting this observation, Guenova and colleagues found a strong Th2 bias in both benign (non-clonal) and malignant (clonal) T cells derived from L-CTCL patients, as gauged by the elevated production of Th2 cytokines, including IL-4 and IL-13, and reduced Th1 cytokine production, including IFN-γ. High constitutive expression of IL-13 and its receptors, IL-13Rα1/2 has been detected in tumor cells derived from CTCL skin lesions and found to mediate tumor cell growth, proliferation, and anti-tumor type I immune response [60,70]. Although the propensity for Th2 bias in benign T cells is intriguing, it reflects the skewing of the entire T cell population, leading to the overproduction of Th2 cytokines and abrogation of Th1 responses. Further, the authors proposed that the Th2 bias of malignant T cells is intrinsic and fueled by cellular abnormalities or the secretion of autocrine growth factors, whereas the bias of non-clonal benign T cells is extrinsic and influenced by the production of Th2 cytokines by the malignant clones. The latter finding was derived from the recovery of Th1 responses (increased IFN-γ production and decreased IL-4 production) on culturing non-clonal benign T cells separately from their malignant clonal counterparts [60].

2.1.1. Role of pro-inflammatory cytokines in CTCL

Besides the secretion of Th2 cytokines, several studies have identified increased expression of pro-tumorigenic/inflammatory cytokines, such as IL-10, IL-15, IL-16, IL-17A, IL-17F, IL-22, and IL-32 in CTCL lesions [57,61]. These cytokines have been shown to exhibit pleiotropic immunosuppressive activities associated with immunodeficiency and evasion of immunologic tumor surveillance. They also possessthe capacity to promote the formation of pro-tumorigenic inflammatory environments, facilitating tumor progression. For example, in SS, activation of the JAK/STAT3 pathway in malignant T cells, with a functional Treg phenotype, leads to the secretion of the immunosuppressive cytokine IL-10 that abrogates the growth of non-malignant T cells [71]. Malignant clones in L-CTCL patients express elevated levels of IL-10, which reduces Th1 cytokine production and diminishes Th1 responses [60]. Recently, Wu et al. [72] demonstrated the pivotal role of IL-10, secreted by host cells, in maintaining large numbers of infiltrating macrophages and their M2 polarization in the TME of T cell lymphoma. Using xenograft mice models, the group also determined the critical contribution of IL-10 in facilitating CTCL tumor growth. IL-10 secretion by malignant T cells has been found to impair the differentiation of infiltrated monocytes into mature dendritic cells (DCs), thereby compromising the competent host anti-tumor immune response [73]. Expectedly, a stage-dependent increase in IL-10 mRNA expression, with a collateral increase in the density of malignant T cell infiltrates, has been observed during MF progression from patch to tumor stage [55,72]. Similarly, a progressive increase in the mRNA expression of IL-32 in MF skin lesions [74] and its overexpression in SS patients has been reported [29]. Very recent observations have suggested significantly upregulated expression of IL-32 between MF lesional fibroblasts and fibroblasts in healthy skin [75]. IL-32 is an autocrine cytokine that has been demonstrated to stimulate cell proliferation and viability through mitogen-activated protein kinase (MAPK) and NF-κB signaling [76] as well as upregulate the expression of survival genes in MF [74], thus implicating its role in the formation and maintenance of CTCL skin lesions [76]. In contrast to IL-32, there are conflicting reports on the expression and functional role of IL-15 in CTCL. For instance, Willerslev-Olsen et al. [77] demonstrated high, spontaneous IL-15 mRNA expression in malignant T cells versus non-malignant T cells as well as confirmed its constitutive expression in MF skin lesions *in situ* (in agreement with the findings in [78–80]); however, the authors found no correlation with advanced or progressive disease. Mishra et al. [81], on the other hand, determined a stage-dependent overexpression of IL-15 in dermal CD4+ T cell infiltrates and circulating CD4+ T cells in peripheral blood obtained from CTCL patients. In CTCL, IL-15 harbors a complex functional profile and has been assigned both anti-tumor [82–84] and tumor-promoting roles [80,85] that are speculated to depend on the cytokine environment and skin lesions being analyzed [77]. The active role of IL-15 in attracting CD4+ memory T cells to the skin and inciting T cell proliferation/survival could be one possible explanation for its high expression in malignant T cells [78,86,87]. Recently, Mishra and team [81] delineated a causal role of IL-15 in CTCL pathogenesis and outlined an oncogenic autoregulatory loop underscoring its overexpression in CTCL patients. According to the proposed model, IL-15 promoter hypermethylation within the Zeb1 (transcriptional repressor of IL-15 in T cells) binding region results in the impaired transcriptional regulation and aberrant production of IL-15 by CD4+ T cells. The resulting autocrine overproduction of IL-15 and downstream signaling in T cells upregulates the expression of chromatin modifiers histone deacetylase (HDAC) 1 and 6 and activates onco-miR-21 via inhibiting HDAC1-mediated negative autoregulatory loop. Dysregulated expression of these enzymes ultimately provokes malignant transformation of normal T cells. In CTCL skin lesions, epidermal keratinocytes (KCs) that are triggered by malignant T cells express IL-15 *in situ*, proving that

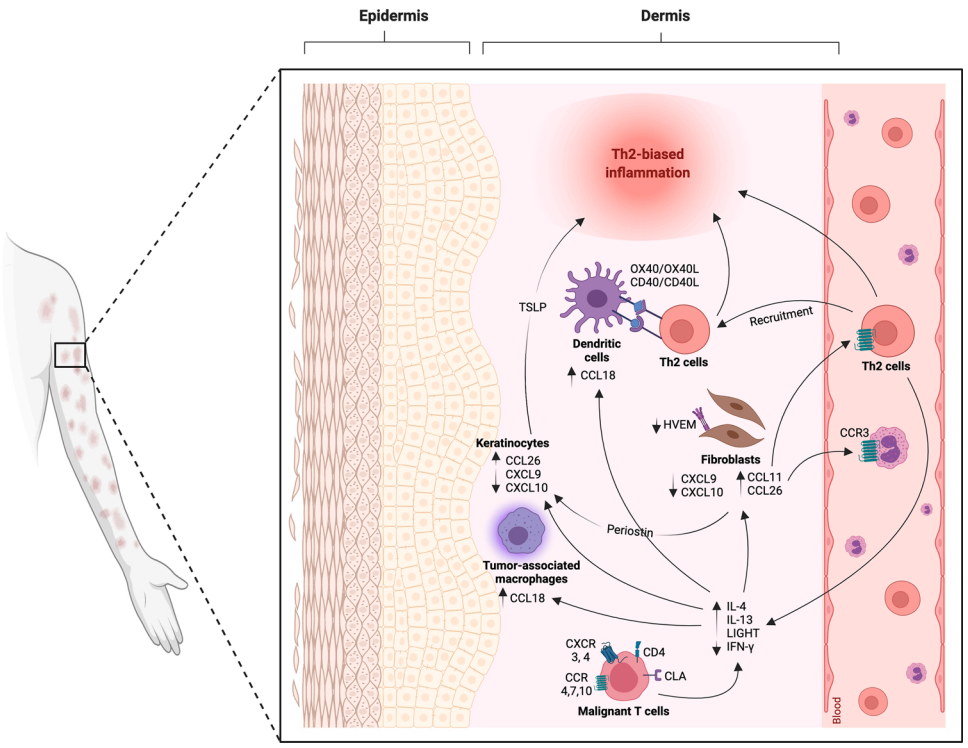

Fig. 1. Role of cytokines in the development of a Th2-biased inflammatory milieu through the modulation of chemokines.
In MF/SS, CLA+ CD4+ malignant T cells express various but limited numbers of chemokine receptors such as CXCR3, 4, and CCR4,7,10. Increased expression of Th2 cytokines such as IL-4 and IL-13 by malignant T cells stimulates the secretion of Th2-recruiting chemokines CCL26 and CCL11 by dermal fibroblasts, CCL26 by keratinocytes, and CCL18 by dendritic cells and tumor-associated macrophages. The production of CCL18 by dendritic cells leads to the recruitment and activation of Th2 benign T cells via OX40/OX40L dendritic cell interactions and CD40/CD40L interactions involving both dendritic cells and malignant T cells. The interactions between Th2 cytokines and CCR3 present on eosinophils and a subset of Th2 cells regulate the Th2-biased inflammatory environment. Th2 cytokines encourage dermal fibroblasts to secrete periostin, which causes epidermal keratinocytes to produce TSLP, that facilitates the skewing of a Th2-polarized inflammatory environment. Decreased expression of IFN-γ by malignant T cells, combined with low expression of HVEM on the surface of dermal fibroblasts, reduces fibroblast and keratinocyte expression of Th1 cell-attracting chemokines CXCL9 and CXCL10. . Increased skin trafficking and activation of Th2 cells, increased levels of Th2 cytokines, and decreased recruitment of Th1 cells contribute to the development of a Th2-biased tumor microenvironment.

malignant T cells are not the exclusive source of IL-15. This is indicative of the strategy adopted by malignant T cells to promote their own proliferation by stimulating IL-15-producing KCs [45,80]. Recent observations have indicated that IL-17F, a member of the IL-17 cytokine family, is expressed constitutively in MF-associated malignant T cells [88] and has been linked with the progressive disease state [89]. Increased IL-17F expression has been found to be induced by the JAK/STAT3 pathway in malignant CTCL cells [89]. Deriving from IL-17′s dominant role in controlling systemic levels of inflammatory and angiogenic factors in a variety of tumor types [90], Lauenborg et al. [88] illustrated IL-17F-driven angiogenesis in MF characterized by enhanced endothelial sprouting and tube formation via activation of endothelial cells. Evidence suggests that IL-16, a T cell chemoattractant and growth factor, potentiates the proliferation, migration, and cutaneous accumulation of C-C Motif Chemokine Receptor (CCR)4+/Thymic stromal lymphopoietin receptor (TSLPR)+/CD4+/CCR7-/CD31+ effector memory T cells in MF [91]. Besides its modulatory effects on T cells, IL-16 secreted in the cytokine milieu has also been shown to augment the growth and survival of SS cells [91]. Given its role as a modulator of T cell activation and migration, both intracellular and nuclear pro-IL-16 levels were found to correlate with disease stage; early stage CTCL displayed higher plasma levels of secreted mature IL-16, whereas advanced stages were associated with the loss of intracellular IL-16 and surface CD26 levels [259]. Ito et al. [92] determined the aberrant overexpression of IL-22 and a subunit of its specific receptor complex, interleukin-22 receptor subunit alpha-1 (IL22RA1) in advanced CTCL cells. The group described an autocrine pathway initiated by the IL-22-IL22RA1 axis that activates intragenic C-C Motif Chemokine Ligand (CCL) 20 expression, which in turn enhances the multidirectional migratory potential of CTCL cells and facilitates invasion and distant organ metastasis via CCR6 chemokine receptor interaction. The findings were in concert with previous studies associating elevated CCL20 with epidermal hyperplasia and the infiltration of CCR6+ cells such as Langerhans cells into CTCL lesional skin [61]. Assessment of the IL-22/IL-17 involvement and their corresponding signature molecules has linked IL-22, and not IL-17, with the development of CTCL [61]. Recent investigations aimed at deciphering the underlying mechanisms of pruritus and disease severity in CTCL patients have suggested a potential role for the Th2-associated cytokine IL-31. IL-31 is a novel cytokine that belongs to the glycoprotein 130 (gp130)/IL-6-derived cytokine family and is primarily produced by skin-homing CD4+ Th2 cells [93]. Widely recognized as a pruritogenic cytokine, IL-31 has been identified as a link between the immune and neuronal systems and, hence, is strongly associated with allergic or pruritic disorders such as atopic dermatitis and atopic eczema [94,95]. Beyond itch, emerging data has elucidated the immunomodulatory and pro-inflammatory functions of this cytokine, particularly, in Th2-biased inflammation [95]. In addition, IL-31 has been implicated in regulating epithelial barrier function, neuronal development, as well as cellular properties such as differentiation, migration, proliferation, and survival through the IL-31/IL31RA/OSMRβ axis and the downstream activation of canonical JAK/STAT, Phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt), and MAPK pathways [96,97]. In CTCL, the exact pathological function of IL-31 remains elusive and discrepant. Studies delineating the functional role of IL-31 in CTCL have documented variable findings on the correlation between IL-31 levels with that of pruritus and disease severity. Although raised serum levels have been found to positively correlate with CTCL severity and marked pruritic symptoms [98,99], differences in IL-31 serum levels with no or marginally detectable expression have been reported in non-pruritic (MF) and pruritic (Folliculotropic MF (FMF) and SS) CTCL variants, respectively [100].

In conjunction with the Th2 cytokine-mediated immune shift accompanying disease progression, CTCL patients with a high-burden (detectable levels of circulating malignant T cells) disease manifest

altered profiles of secreted Th1 cytokines and immune function abnormalities. Stage-related defects in cell-mediated immunity and that of Th1 cytokine production, associated with progressive SS, have been found to be coherent with the decreased secretion of IL-12 [101]. Studies have demonstrated the decreased ability of SS-borne peripheral blood mononuclear cells (PBMCs) to produce IL-2 [102] and IL-12. IL-12 is a classified immunoregulatory cytokine that potently induces the production of IFN-γ and activation of cytotoxic lymphocytes [103]. In addition to PBMCs, CD7- (lack of CD7 surface expression in CD4+ T cells) and CD7+ T cell subset have been found to synthesize IL-2 in SS and MF patients, respectively [104]. Aside from PBMCs, a progressive decline in the production of IL-12 and IFN-α by CD123+ myeloid dendritic cells (DC1) and CD11c+ plasmacytoid dendritic cells (DC2) [105], respectively has been observed [101]. The drop in the production of these cytokines, crucially linked to Th1 responses, coincide with an increase in tumor burden in peripheral blood and a diminution of DC numbers in the circulation. Profound alterations in the regulation and expression of cytokine genes in activated PBMCs, associated with early to late-stage MF (with and without blood involvement), have also been observed and proposed to underscore inherent defects in immunocompetence in patients [106]. In SS patients, a dysfunctional cytokine response, including impaired secretion of IL-6, IL-10, and IL-13 and decreased production of type 1 interferons (IFN-α, β), in PBMCs has been attributed to both extracellular and intracellular toll-like receptor (TLR) activation [107]. Intriguingly, unlike the Th2 bias of malignant T cells seen in SS patients upon TLR activation, mononuclear cells do not show enhanced Th2 cytokine secretion. This suggests that TLR-pathogen-associated molecular pattern (PAMP) interactions generate Th1 and not Th2-related cytokines [107]. These results signify the role and involvement of different cell types and the immunological milieu in the development of CTCL-associated cytokine disorders and stage-related defects in cellular immunity. Benefitting from such observations, reconstitution of Th1 cytokines, like IFN-α and IFN-γ, and restoration of Th1 responses seems to be an effective treatment strategy for CTCL patients.

2.2. *Role of chemokines in Th1/Th2 transition and immune cell trafficking in CTCL*

Parallel to the alterations in malignant cytokine expression pathways and their skewing towards a Th2 profile, changes in chemokine expression patterns have been implicated in fostering a Th2-biased inflammatory environment in CTCL. Evidence suggests that changes in malignant Th1 and Th2 cytokine secretion can affect chemokine secretion by fibroblasts, DCs, tumor-associated macrophages (TAMs), and KCs [44] (Fig. 1).

In early stage CTCL, KCs and dermal fibroblasts in the lesional skin express higher amounts of the chemokines CXCL9 and CXCL10 that are involved in preferentially attracting Th1 cells to the inflammatory sites. In advanced stages, however, there is a strong reduction in Th1-associated chemokine expression levels, with an increase in the expression of Th2 cell-attracting chemokines such as CCL17, CCL18, CCL22, and CCL26 [91,108–111]. Underlying the decreased expression of Th1 chemokines in advanced CTCL is the low expression of herpesvirus entry mediator (HVEM)/CD270 on the surface of dermal fibroblasts that can contribute to the shift from Th1- to Th2-dominant TME during disease progression [109]. HVEM is one of the three distinct receptors for the cellular ligand LIGHT/CD258 [112], a member of the tumor necrosis factor (TNF) superfamily which is expressed on immature DCs and activated T cells [113,114]. In the CTCL setting, LIGHT-HVEM interaction enhances the production of chemokines that are involved in recruiting CXC chemokine receptor (CXCR) 3+ Th1 cells, such as CXCL9−11 by IFN-γ-stimulated dermal fibroblasts through inhibitor κBα (IκBα) phosphorylation and downstream activation of NF-κB. With disease progression, though, a decrease in CXCR3 ligands and downregulation of HVEM expression alongside elevated LIGHT expression potentially affects the Th1 chemokine pattern and the Th1-Th2 balance [109]. In contrast to IFN-γ, IL-4 (expressed by tumor cells)-stimulated dermal fibroblasts in the lesional skin express higher mRNA levels of Th2-recruiting chemokines CCL26 (also known as eotaxin-3) and CCL11 (also known as eotaxin-1) in comparison to normal skin [110]. In addition to the higher levels of these Th2 chemokines, the lesional skin of advanced CTCL displays upregulated mRNA expression of CC chemokine receptor 3 (CCR3), an eotaxin

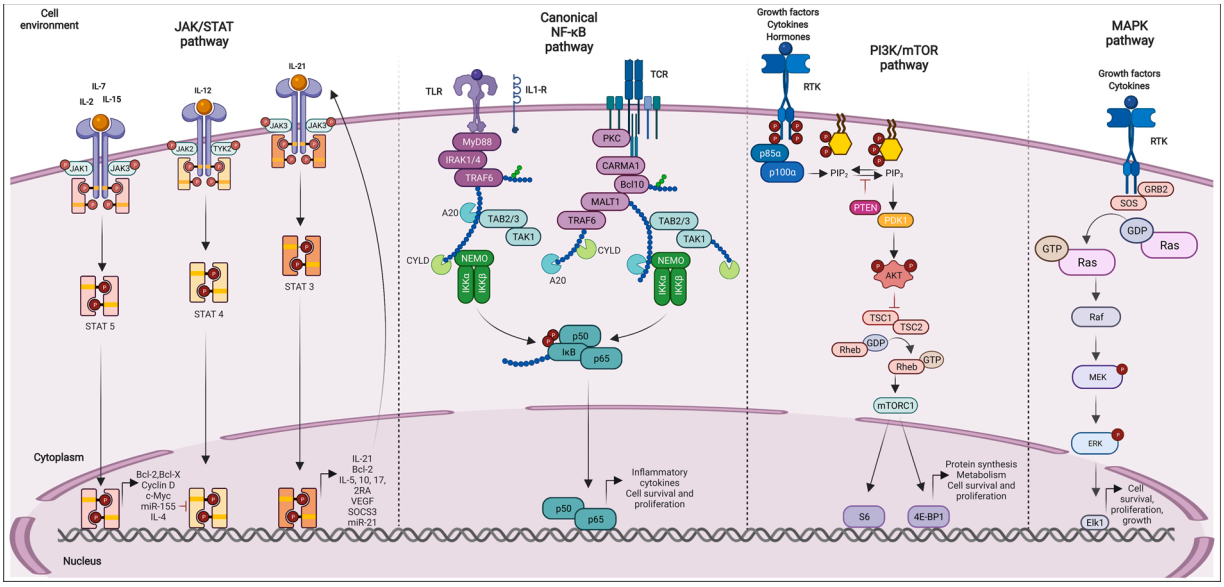

Fig. 2. Spectrum of recurrently mutated signaling pathways in CTCL.
CTCLs show aberrant activation of an array of signaling pathways, including JAK/STAT, NF-κB, PI3K/mTOR, and MAPK pathways. Activation of these pathways, elicited upon interaction between soluble ligands (cytokines and growth factors) or cell antigens and their cognate receptors, results in the translocation of effector proteins into the nucleus and transcription of specific genes that regulate inflammation, immune response as well as T cell activities such as cell proliferation, survival, growth, and distinct lineage differentiation.

receptor present on eosinophils and a subset of Th2 cells [115,116]. The interaction between eotaxins and CCR3 has been implicated in regulating the Th2-biased inflammatory environment crucial for the development of CTCL. Moreover, Th2 cytokines have been demonstrated to enhance the secretion of CCL18 that is expressed by TAMs [117–119] and DCs [108] in CTCL skin. CTCL skin lesions typically exhibit increased expression of CCL18 that is specifically involved in recruiting benign, infiltrating Th2 cells [120] and correlate with disease progression [108,118]. In a recent investigation, Vieyra-Garcia et al. [120] unveiled the presence of an inflammatory synapse between CCL18-expressing OX40L+/CD40L+/c-Kit + DCs, benign Th2 T cells, and malignant T cells. According to their model, the production of CCL18 by c-Kit+ DCs leads to the recruitment and activation of Th2 benign T cells via OX40/OX40L DC interactions and CD40/CD40L interactions involving both DCs and malignant T cells. This activation of benign T cells ultimately causes apparent (increased) inflammation in the CTCL skin and has been postulated to provide pro-growth signals to the tumor.

Thymic stromal lymphopoietin (TSLP) is a cytokine that activates CD11c (+) DCs and triggers Th2-type immune responses and inflammation [121] via the synthesis of Th2 chemokines such as CCL17 (also known as thymus and activation-regulated chemokine (TARC)) and CCL22 (also known as macrophage-derived chemokine (MDC)) [122,123]. Takahashi et al. [121] determined a reinforcing cycle linking Th2-type immune response and TSLP production by KCs that is stimulated by an ECM protein periostin produced by dermal fibroblasts in CTCL pathogenesis. Particularly, the authors decoded the important roles of periostin and TSLP in establishing Th2-dominant TME in CTCL, as determined in atopic dermatitis [124]. Serum [125] and plasma [91] TSLP levels in CTCL patients are elevated in comparison to the levels in serum from healthy controls, suggesting that Th2-dominant environment in CTCL lesions may be driven by TSLP.

2.2.1. *Role of chemokines in malignant T cell trafficking in CTCL*

In addition to their central role in Th2 transition, chemokine/chemokine receptor networks coordinate the localization/trafficking of immune cell subsets within the microenvironment of skin tumors, particularly CTCL that arise from the malignant proliferation of skin-homing T cells [8,126]. Within the TME, host stromal and cancer cells produce various chemokines that stimulate directional migration and activation of TILs and innate immune cells [127–129]. T cells belonging to distinct T cell lineages display different chemokine receptor expression patterns that account for their differential responses to specific chemokines [130] and different migratory properties [131]. For instance, polarized T cells harbor distinct profiles of chemokine receptors that are influenced by cytokines IFN-α and transforming growth factor beta (TGF-β): Th1 polarized cells show 'preferential' expression of CXCR3, CXCR6, and CCR5 while Th2 subset have 'preferential' expression of CCR4 and CCR8 [132]. Such flexibility in chemokine receptor expression serves tissue-selective migration of effector T cells. Besides the well-characterized chemotactic functions, chemokine receptor/ligand pairs have been assigned several non-redundant roles, including organotropic metastasis and conferring survival advantages to malignant T cells through the activation of PI3K and Akt pathway [133].

CTCL-associated malignant T cells as well as tumor cells express chemokine receptors (albeit, limited) that pair with chemokines produced by endothelial cells (ECs), activated KCs, and DCs. This chemokine receptor-ligand interaction results in the firm arrest of malignant T cells on the luminal surfaces of vascular ECs and migration to specific compartments of the skin such as the epidermis and towards activating DCs, respectively [130,134]. For example, selective expression of CCR4 and CCR10 (receptors for CCL17 and CCL27, respectively) on skin-homing memory T cells serves as an important regulator of effector T cell recruitment to the skin [135,136]. A role for the CCR4−CCL17, CCL22 interactive pathway in T cell homing to skin has been suggested by a report showing an increased percentage of skin-homing (Cutaneous Lymphocyte-associated Antigen (CLA)+/CCR4+) T cells in the lesional skin and peripheral blood of CTCL patients, parallel to the elevated expression of CCL17 and CCL22 in CTCL skin [137]. It has been shown that enhanced CCL22 expression by Langerhans cells in the epidermal compartment of CTCL lesions mediates the positioning and clustering of malignant CCR4+ T cells in the skin, resulting in the formation of hallmark Pautrier's microabscesses or intraepidermal clusters of atypical lymphocytes in MF [137].

Beyond T cells, CTCL cells have been found to adopt the CCR4-mediated multistep adhesion cascade to migrate [138]. Wu et al. [138] demonstrated that differential expression patterns of CCR4 as well as differential functional capacities of CCL22 and CCL17 mediate CCR4-driven transendothelial migration in both MF and SS cells. Specifically, the group found that MF cells are more responsive towards CCR4−CCL22 signaling and, hence, manifest greater chemotaxis, integrin-mediated arrest on ECs, and overall transendothelial migration in comparison to SS cells [138]. Analogous to the differential expression on neoplastic cells, CCR4 expression patterns in reactive T cells also differ with disease stage. Substantially higher expression of CCR4 is observed in the early patch and plaque stages of MF [139]. Serum CCL17 levels, however, tend to be higher in the MF tumor stage than in the patch/plaque stage [140]. Like CCR4, both tumor and reactive T cells, associated with the MF patch and plaque stage, express CXCR 3/CD183 and CXCR4 [139,141]. Higher CXCR3 levels were specifically associated with epidermotropic histologic pattern-bearing (low-grade) tumors vs. dermal pattern-bearing tumors in MF cases [141]. Alongside CXCR3, increased expression of its ligands CXCL9 and CXCL10 has been detected in early stage MF and is implicated in facilitating recruitment and aggregation of tumor cells in the skin [141]. Circulating SS cells and skin-infiltrating malignant T cells have also been shown to express functionally active CXCR4, a receptor for CXCL12/stromal cell-derived factor 1 (SDF-1) that is abundantly synthesized in the skin [142]. In SS, the CXCR4-CXCL12 axis plays a significant role in SS cell skin recruitment and accumulation, mediated through the downregulation of CD26/dipeptidyl peptidase IV (DPPIV) [142]. CXCL12 is a selective substrate of CD26/DPPIV, a membrane-bound extracellular peptidase known to alter the chemotactic behavior of chemokines through catalytic N-terminal truncation [143]. Additionally, tumor MF cells display high levels of the lymph node-homing molecule CCR7 [144] that coordinates the migration of mature dermal DCs and selected T cell subsets into lymphatic tissue [145]. SS-associated skin-homing T cells have also been found to express fairly high levels of CCR7 [146] which is proposed to direct their tropism and lymphoid organ infiltration [130].

Taken together, chemokines and their cognate receptors appear as multifarious molecules that critically contribute to the characteristic features of CTCL - skin-tropism and Th2-dominant TME. Detailed understanding of how the chemokine system influences T cell migratory patterns and mediates other non-classical cellular functions is instrumental to designing strategies that can interfere with this system for therapeutic purposes, since chemokine-targeting biologics are already in development for inflammatory skin diseases.

3. Dysregulated signaling pathways in CTCL

In the past three decades, significant progress has been made in delineating the molecular pathogenesis of CTCLs by employing various cytogenetic tools. Large-scale genome studies and sequencing technologies have uncovered a comprehensive landscape of genomic and epigenetic modifications that represent one of the important protumorigenic principles in CTCL initiation and progression. Recent DNA and RNA sequencing studies have unveiled dysregulation of an array of signaling pathways downstream of the genomic events, including JAK/STAT, NF-κB, PI3K/mTOR, and MAPK pathways, that contribute to the oncogenesis and heterogeneity of T cell malignancies [14,147] (Fig. 2). In addition, since the progression of CTCL involves a complex interplay between malignant T cells, stromal, and epidermal

components of the TME, aberrant alterations in signaling pathways through autocrine or paracrine stimulation of TCRs by cytokines, ILs, or growth factors produced by malignant T cells and/or TME can dysregulate T cell signaling and thus modify cellular interactions in the CTCL microenvironment.

3.1. JAK/STAT pathway and CTCL

The JAK/STAT pathway is a potent signaling cascade that is central to cytokine stimulation in T cells [148]. Apart from cytokine signaling, the JAK/STAT axis serves as an intracellular mediator of metabolically relevant hormones and growth factors associated with crucial cellular events [149]. The mammalian JAK family consists of four cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3, and Tyrosine kinase (TYK) 2 [150] whereas the STAT family consists of seven latent cytoplasmic proteins: STAT1−4, STAT5A/B, and STAT6 [151]. These proteins are ubiquitously expressed, share structurally and functionally defined domains, and form different combinations that hold a high degree of specificity towards specific cytokines or growth factor signals [152–154].

Theoretically, the core JAK/STAT pathway is relatively simple and straightforward. However, the biomolecular effects associated with the activation of this pathway are complicated [155]. This pathway is upstream of multiple complex biological processes such as inflammation, development of the immune system, and immune response [156]. It is one of the 12 core cancer signaling pathways that confers a selective growth advantage to cancer cells by regulating cell survival [157]. Abnormal activation of the JAK/STAT pathway is ubiquitous in all T cell malignancies [148]. In particular, dysregulation of the JAK3 signaling axis and the activation of its downstream proteins/transcription factors such as STAT3, STAT5, and STAT6 have been associated with cytokine-mediated control over proliferation and apoptosis-resistance in malignant T cells [34,70,158,159]. In CTCL, altered activation of several STAT proteins has been reported and is implicated in driving early and advanced stage disease. The early stage of CTCL is generally typified by activated STAT signaling that is induced by IL-2, IL-7, and IL-15 cytokines [160] while the advanced stages are defined by cytokine-independent JAK1 and JAK3 constitutive signaling [161]. Early and late CTCL stages have been reported to have constitutive activation of STAT4/5 and STAT3, respectively [159]. In comparison to non-malignant skin, lesional skin derived from early CTCL cases exhibits overexpression of STAT4 [162], a protein involved in IL-12-directed Th1 response [163]. During the late stage, however, STAT4 expression is lost, consequently leading to decreased responsiveness to IL-12 and the acquisition of a Th2 phenotype [163,164]. Previous studies have demonstrated marked defects in IL-12 p70 production by monocytes in SS patients [165]. Several molecular mechanisms mediating STAT4 downregulation have been identified [165,166], including aberrant histone acetylation [162] and indirect control by constitutively activated STAT5 [167]. Activation of STAT5, also known to occur in late stage CTCLs [159], has been shown to upregulate the expression of anti-apoptotic genes (Bcl-2 and Bcl-x), cell cycle genes (Cyclin D and c-Myc), Th2 cytokines (IL-4), and oncogenic miRNA-155 . STAT4 is a known target of miR-155 [162] and, hence, loss of STAT4 expression and impaired Th1 response has been attributed to STAT5-mediated upregulation of miR-155 [159]. Research has also unveiled an inverse relationship between STAT4 and STAT6 expression levels in malignant CTCL cells. Litvinov et al. [162] recorded STAT6 upregulation as a sequel to downregulated expression of STAT4 in CTCL cells and described its potential to affect the Th1/Th2 balance. The malignant infiltrate obtained from CTCL skin biopsies was found to have elevated pSTAT6 expression as well as significant numbers of pSTAT-6+ mononuclear cells. In line with the STAT6 activation seen in advanced stages, stage IV CTCL patients were reported to harbor more pSTAT6+ cells than stage I patients [70]. Constitutively activated in malignant lymphocytes in MF/SS patients, STAT6 is a multifarious protein associated with cell-cycle progression, genomic stability, production of Th2 cytokines, chemotaxis, and anti-tumor immune response [34]. STAT6 has also been considered as a common mediator of the IL-13/IL-4 signaling pathway implicated in tumor cell proliferation [70].

In addition to STAT5, advanced stages of CTCL are defined by constitutive STAT3 activation [159,168]. Several molecular evidences have been presented to support this observation, including stimulation by IL-7 and IL-15 [169], IL-21 autocrine feedback loop in the micromilieu of CTCL cells [170], and/or constitutive activation of JAK1/JAK3 signaling [160,161,171]. Activated STAT3 has been found to participate in oncogenic transformation by regulating survival signals such as Bcl-2 expression [161], promoting Th2 and Th17 phenotypes, and inducing the expression of oncomiR miR-21 [172]. In addition, it has been implicated in upregulating the expression of potent angiogenic factor vascular endothelial growth factor (VEGF) [173], IL-5, IL-10, and IL-17 [36,162], IL-2RA (α-chain of the IL-2 receptor) [170], and suppressor of cytokine signaling-3 (SOCS-3) [174]. Aberrant SOCS-3 expression, which is dependent on the activation of fully functional STAT3, has been linked to malignant transformation that is initiated via eliciting a change in the sensitivity of cytokine receptors or altering the balance between different cytokine responses, including IFN-γ and IFN-α [174,175]. Evidence has also suggested the functional relevance of the STAT3/CCL20/CCR6 axis in CTCL cell metastasis [176]. Notably, STAT3 has been identified as an important mediator of phenotypic plasticity in CTCL owing to STAT3-dependent secretion of IL-17 in CTCL cell lines [64]. Using organotypic mouse models, Thode et al. [45] determined the potential of malignant T cells to cause KC hyperproliferation and dedifferentiation and induce disorganized KC stratification through the secretion of galectin-1 and -3 which drive STAT3 and ERK1/2 signaling pathways. Beyond miR-155 and miR-21, constitutive activation of STAT signaling and abnormal regulation of STAT3/5 have been shown to enhance the expression of oncomiRs such as miR-93 and miR-214 [167,172,177] as well as repress the expression of tumor suppressor miRs such as miR-22 in CTCL-derived malignant T cells [178]. Changes in the expression of these miRNAs appear to facilitate oncogenesis, either directly by promoting proliferation/survival of malignant T cells or indirectly via modulating the TME and anti-tumor immune response [167,177]. This modulation of alternative pathways through miRNAs signifies the versatile nature and the crucial role of the JAK/STAT signaling axis in intracellular crosstalk [156].

The canonical mode of JAK/STAT signaling is well-known and based on STAT phosphorylation by activated JAK. In the past few years, divergences in this traditional paradigm have been reported, including the non-canonical functions of the signaling components [179] and their control over the cellular epigenetic status [180]. Very recently, Vadivel et al. [181] provided supporting evidence for the non-canonical (cytokine receptor-independent) functions of JAK3 in CTCL by demonstrating its ectopic nuclear expression and interactions with nuclear protein POLR2A, the catalytic active subunit A of RNA Polymerase II in malignant T cells. The authors also established the capacity of nuclear JAK3 to modulate tyrosine phosphorylation of Histone H3; however, its capacity to epigenetically regulate gene transcription in malignant T cells currently remains unknown. Other studies with the common aim have shown that continuous activation of STAT3 induces the expression of DNA methyltransferase 1 (DNMT1) in malignant T cells and thus mediates oncogenic cell transformation via DNA methylation and epigenetic gene silencing of tumor suppressor genes [182]. A member of the DNMT family of enzymes, DNMT1 is the major catalytic player in DNA methylation inheritance and epigenetic gene silencing [183].

Studies concentrating on the involvement of the common cytokine receptor chain (c)-associated JAK/STAT pathway in lymphomagenesis have reported its activation in CTCL cells. In low-grade CTCL cases, this activation is induced by γ-chain-signaling cytokines lL-2, -4, -7, -9, and -15, whereas in advanced cases, the activation appears constitutive, in part, due to the lack of SHP-1 phosphatase-mediated negative regulation [184]. Environmental factors such as staphylococcal enterotoxin A (SEA)-producing *Staphylococcus aureus*, isolated from the infected skin of

CTCL patients, has been shown to contribute to CTCL aggravation and progression via crosstalk-dependent STAT3 activation and IL-17 expression in SEA-responsive non-malignant infiltrating CD4+ T cells [185]. This IL-17A response was discovered to be influenced, partly, by IL-2 receptor common γ-chain cytokines that govern the toxin-mediated interactions between malignant and non-malignant T cells. Implicated both as an etiological agent and a cause of significant morbidity, microbes such as *Staphylococcus aureus* cause recurrent skin and life-threatening systemic infections in 44–76 % of patients with advanced stage CTCL [185]. Genetic alterations potentially affecting the JAK/STAT pathway including GCNAs and SNVs of JAK2 [25], activating mutations in JAK3, SOCS1 amino acid changes [186], somatic mutations in JAK1 [187], and copy number gains of STAT3 and STAT5B [31] have all been reported and proposed as disease mechanisms in CTCL.

3.2. PI3K/mTOR signaling pathway and CTCL

The PI3K/Akt/mammalian target of rapamycin (mTOR) pathway is a critical regulator of cell growth, proliferation, migration, apoptosis, cell cycle progression, and cytoskeletal rearrangement [188]. Dysregulated in a wide variety of human cancers, constitutive activation of the PI3K/Akt/mTOR pathway [189] due to the mutational loss of its negative regulator, phosphatase and tensin homolog (PTEN), is frequently found in T cell malignancies [189–191]. In SS, multiple components of the PI3K/Akt cascade have recurrent genomic copy number variants (CNVs), such as copy number (CN) loss of LKB1/Serine/Threonine Kinase 11 (SK11), PTEN, and programmed cell death 4 (PDCD4) and gains of P70S6K. These alterations underlie the dysregulation of the PI3K/Akt/mTOR pathway as well as define the outcome and survival classes in SS patients [192]. Whole exome sequencing of 25 SS cases has confirmed somatic copy number alterations (chromosomal deletion) in PTEN [28]. Such genomic dysfunction, mapped onto recurrently unbalanced 10q23 and 17q23 loci [193], potentially result in a metabolic shift toward aerobic glycolysis and aberrant mammalian target of rapamycin complex 1 (mTORC1)-dependent protein synthesis that is beneficial (in terms of energy) for SS cell recruitment to skin and/or lymph node [192]. Besides altering cellular bioenergetics, defects in mTORC1-dependent protein synthesis have also been found to increase SS cell size and generate larger cell dimensions, a phenomenon termed 'large cell transformation (LCT)'. In LCT, malignant small lymphocytes undergo cytologic transformation and adopt a clonally identical large cell phenotype [194] which is associated with an aggressive clinical course and poor prognosis [195]. Parallel analysis of SS cells derived from skin and blood, concurrently acquired from SS patients, has shown higher mTORC1/mTORC2 activation in skin-derived cells when compared to corresponding circulating SS cells [192]. Beyond genetic alterations, aberrant activation of the PI3K/mTOR pathway has also been attributed to microenvironmental signals generated by malignant T cell activation and chemokine and cytokine secretion [86,192]. In particular, SDF-1 and CCL21 chemokines have been shown to activate the mTORC1 pathway in CTCL through signaling via CXCR4 and CXCR7 receptors that participate in SS cell skin- [142] and lymph node-homing [192,196,197].

Besides SS, oncogenic activation of the PI3K/mTOR signaling cascade is frequently observed in MF [198]. *In situ* immunohistochemical assessment of the expression status of the PI3K/mTOR pathway components such as p-Akt, p-70S6K, and eukaryotic initiation factor 4E binding protein 1 (p-4E-BP1) as well as that of p-extracellular signal-regulated kinase (ERK)1/2, p-STAT3, and Notch homolog 1 (NOTCH1) in MF patients has revealed a close interaction of the Akt/mTOR pathway with that of p-ERK, p-STAT3, and NOTCH1 [198]. This association has been implicated in disease progression and the aggressive phenotype in MF cases. Specifically, expression of p-4E-BP1, p-p70S6K, and NOTCH1 was found to positively associate with advanced MF stages, whereas simultaneous overexpression of p-Akt, p-p70S6K, and p-4E-BP1 was determined to adversely affect patient survival [198]. Whole-exome sequencing on 11 MF and SS cases and matched normal samples has led to the identification of somatic alterations in PI3K-related genes involved in TCR-CD28 signaling [27]. Moreover, the p.Arg297Cys mutation in phosphatidylinositol-3,4,5-trisphosphate dependent rac exchange factor 2 (PREX2, referred to as PREX2a), a PI3K-interacting oncoprotein [199] that inhibits PTEN [200], has been identified in MF samples [28]. PTEN mutations and their correlation with disease- and progression-free survival in tumor stage have been reported in MF cohorts [201]. Similar to SS, PTEN deletion and the consequent loss or decreased functional PTEN protein have also been recorded in MF samples and postulated to underscore Akt activation in most (if not all) MF cases [201]. Also, in advanced MF stages, a cytoprotective signaling loop has been identified involving overexpression of miR-122 in malignant T cell infiltrates that amplifies the anti-apoptotic Akt/p53 signaling circuit and decreases sensitivity to chemotherapy-induced apoptosis [202].

3.3. NF-κB pathway and CTCL

The pivotal role of NF-κB in regulating inflammation relies on its ability to arbitrate the induction of pro-inflammatory genes encoding a wide range of chemokines and cytokines [203] as well as regulate the activation of inflammasomes [204,205]. NF-κB also governs CD4+ T cell differentiation into Th1, Th2, Th17, and T follicular effector T cells that are involved in generating immune responses via the secretion of cytokines [206]. The regulatory effect of NF-κB on CD4+ T cell differentiation is dependent upon its control over cytokine production in innate immune cells and T cell intrinsic factors such as TCR-induced signals [203,207]. Besides its physiologic functions in T cell differentiation and cytokine production, dysregulated activation and constitutive expression of NF-κB have been detected in T cell malignancies, including CTCL. In fact, a recent study has confirmed the activation of NF-κB in both early and advanced MF stages, implicating the role of this prominent cell-survival pathway in disease development and progression [14]. Although the mechanisms that trigger constitutive NF-κB activation are not well-established, studies have acknowledged its seminal role as a mediator between malignant cell survival/proliferation and inflammatory signals [208].

The NF-κB family of transcription factors consist of five proteins: c-Rel, p65 (RelA), RelB, p50 (p105/NFKB1), and p52 (p100/NFKB2) [209] that function as homo- and heterodimers and exhibit transcriptional selectivity towards potential NF-κB target genes [210]. CTCL cells have been shown to express all five Rel family proteins [208], with increased expression of p50, p52, p65, and RelB subunits found in tumor lesions [14]. SS cases typically show canonical NF-κB activation [211] that predominantly activates the p50/p65 dimeric NF-κB complex [212]. SS/CTCL cells also exhibit a constitutive increase in the NF-κB transcriptional activity that accounts for the increased expression of anti-apoptotic genes [212,213] as well as that of pro-inflammatory and anti-inflammatory cytokines [208]. The NF-κB-mediated increase in the expression of anti-apoptotic genes, such as cellular inhibitor of apoptosis protein (cIAP)-1, cIAP-2, and Bcl-2 and pro-inflammatory cytokine genes, such as IL-1, IL-8, tumor necrosis factor alpha (TNF-α), and IL-17 has been linked with the sustained survival and proliferation of malignant CTCL cells [89,208,214,215]. NF-κB family members have also been suggested to regulate the Fas promoter function and, hence, apoptotic sensitivity in CTCL [216]. The Fas (also known as CD95 or APO-1 or TNFRSF6)-Fas Ligand (FasL) pathway serves a crucial part in maintaining immune homeostasis [217]. This is mediated by the elimination of (a) autoreactive T cells formed during lymphoid cell development in the thymus (termed central tolerance) [218] and the periphery (termed peripheral tolerance) [219] and (b) activated T lymphocytes generated during immune response (activation-induced cell death (AICD)). In CTCL, alterations in this pathway via decreased Fas protein expression [220], high Fas promoter methylation [216], or homozygous FAS promoter single nucleotide polymorphisms (SNPs)

[221] have been detected, with implications in CTCL pathogenesis and clinical response [220].

In parallel to the elevated expression of pro-inflammatory cytokines, increased expression of NF-κB-dependent anti-inflammatory cytokine genes IL-10 and TGF-β has been linked to the inherent immunosuppressive nature of CTCL [208]. Studies have identified the role of NFKB1 (p50) homodimers as a transcriptional activator of IL-10 and determined its ability to differentially regulate IL-10 as compared to TNF and IL-12 [222,223]. Such reciprocal modulation of pro- and anti-inflammatory cytokine secretion could also explain the immunosuppressive functions exerted by NF-κB in CTCL. Regardless, the NFκB-mediated transcriptional regulation of immunosuppressive genes remains largely unknown. Genome-level studies aimed at delineating the genomic landscape and mutation patterns in CTCL have identified 17 mutated genes, including those involved in NF-κB signaling [25]. Several genetic alterations, including heterozygous deletions, somatic mutations, truncations, CNVs, and splice site mutations have been reported in NF-κB components such as NFKB2 and caspase recruitment domain (CARD) [25,27–29]. Frequent mutations (truncations and heterozygous deletions) in NFKB2 proto-oncogene in CTCL patients have been associated with constitutive NF-κB activation [25,224]. In 15% of SS patients, gain of function (GOF) mutations in CARD11 (CARMA1) have been documented [28,29]. CARD11 is a multi-domain cytoplasmic scaffold protein and a component of the multimeric CBM signaling complex that relays signaling from TCR, triggering the activation of NF-κB [225]. Of importance, the somatically mutated CARD11 gene has been determined to be a likely cancer driver, indicating its functional impact in CTCL [29]. In addition, 18 % of MF and SS patients have been found to harbor genomic gains and point mutations in TNFRSF1B that encode tumor necrosis factor receptor 2 (TNFR2). Such somatic alterations result in recurrent TNFR2 Thr377Ile mutants in T cells, the expression of which is associated with the activation of non-canonical NFKB2 signaling and enhanced T cell activation and survival [27]. Genetic studies have also identified frequent bi- and monoallelic deletions of the tumor necrosis factor alpha-induced protein 3 (TNFAIP3/A20) gene in a high percentage of SS patients, resulting in the activation of the NF-κB pathway and increased proliferation of normal T lymphocytes [226]. A20 is an intracellular ubiquitin-editing protein and a crucial negative feedback regulator of NF-κB signaling [227]. In T cell-derived diseases such as SS, A20 acts as a tumor suppressor and therefore, its genetic depletion or inactivation might contribute to SS development [226]. Furthermore, CTCL patients show basal activation of protein kinase TAK1 (although counteracted by the MYPT1/PP1 phosphatase complex) that correlates with NF-κB activation [228]. Using *in vitro* and *in vivo* model systems, Gallardo et al. [228] demonstrated the capacity of phosphorylated TAK1 to sustain NF-κB and β-catenin signaling in CTCL cells, thus facilitating cell survival and proliferation. Novel recurrent, GOF mutation in RLTPR (p.Q575E) has also been determined in CTCL and shown to increase the production of IL-2 via TCR-mediated upregulation of NF-κB signaling in activated T cells [229]. RLTPR has been identified as a putative cancer driver that encodes a scaffolding protein involved in coupling CD28 to the CARD11/NF-κB signaling pathway. Thus, when mutated by the p.Q575E alteration, the interaction between RLTPR and the TCR-dependent enzymes is modified, resulting in the activation of the NF-κB signaling cascade [230]. In both mice and humans with RLTPR deficiency, the lack of functional RLTPR molecules has been found to curb the differentiation of CD4+ T cells toward the Th1 and Th17 polarized states, with no impact on Th2 differentiation [230].

3.4. MAPK cascade and CTCL

MAPKs are key signaling elements that serve as an intermediary link between extracellular signals and the machinery controlling basic cellular processes such as cell proliferation, differentiation, migration, apoptosis, and stress responses. The MAPK signaling cascade is activated when diverse inputs are fed into a three-tiered 'core-signaling module' comprising of MAPK kinase kinase (MAP3K), MAPK kinase (MAPKK), and MAPK [231], resulting in the elicitation of appropriate cellular responses [232]. So far, six distinct components of MAPKs have been identified in mammals: ERK1/2, ERK3/4, ERK5, ERK7/8, Jun N-terminal kinase (JNK)1/2/3, and the p38 isoforms α/β/γ(ERK6)/δ [232–235].

The Ras/Raf/MAPK (MEK)/ERK pathway is the most important and best studied MAPK signaling pathway in mammals [231,232]. Dysregulated in almost one-third of all human cancers, including CTCL, alterations in the ERK pathway occur at several levels but have been prominently attributed to the high frequency of activating Ras and B-Raf mutations as found in most cancerous lesions [236]. Mutations in Ras family oncogenes, including $NRAS^{Q61K}$ and $KRAS^{G13D}$ have been detected in advanced stage CTCL patients and are associated with reduced overall survival in comparison to patients without mutations [237]. Oncogenic NRAS (Q61K) mutations instigate hyperactivation of Ras that induces the downstream MEK-ERK signaling cascade [238] and promotes the survival of CTCL cells. Mutations in the MAPK pathway were also recently determined in 50 % of CTCLs, including all the CTCL histological subsets analyzed irrespective of their heterogeneous mutational profile [239]. Besides alterations in the ERK pathway, Bliss-Moreau et al. [240] showed a selective increase in p38γ gene expression *in vitro* and in CTCL clinical samples. P38γ is a crucial regulator of malignant T cell activity and growth as well as CTCL cell viability, implicating its important functional role in CTCL pathogenesis [240].

MAPK pathway activation has also been linked to histone deacetylase inhibitor (HDACi) resistance in CTCL [241]. CTCL cells resistant to epigenetic drug-induced apoptosis exhibit increased MEK phosphorylation and decreased expression of pro-apoptotic Bim. This demonstrates that upregulation of the MAPK pathway is one of the clinical mechanisms underlying resistance to the potent and clinically approved anti-proliferative agents [241].

4. Conclusion and future directions

A growing awareness of the complex dynamics of CTCL arising from genetic diversity, phenotypic variability, and tumoral heterogeneity has clearly expanded over the last few decades. Recent developments and constant optimization of sequencing platforms, such as whole-exome and single-cell analysis tools, are constantly changing the traditional paradigms of CTCL by giving an unprecedented view into tumor evolutionary origins and the unique TME. In the past decade, CTCL tumoral heterogeneity has been extended to include the transcriptomic and clonal diversity of malignant T cells, their interaction with the local microenvironment, and their functional impact on immunological processes during tumor evolution. When combined with comprehensive molecular and immunobiological studies, these findings have provided remarkable knowledge on CTCL immunophenotype and enhanced the understanding of diverse mechanisms that underlie the evolving immunodeficiency routinely observed in CTCL patients. These mechanisms comprise alterations in multiple cellular signaling cascades, constitutive activation of STAT proteins, formation of a Th2-biased inflammatory milieu, malignant secretion of immunosuppressive cytokines and chemokines, loss of TCR repertoire complexity, complex crosstalk amongst malignant T cells and the TME components, and competitive malignant replacement of benign T cells. Identification and in-depth characterization of these regulatory mechanisms have opened new avenues for molecularly targeted therapeutics. In particular, the concept of reinvigorating the host immune response, particularly in an immunopathologically-driven disease like CTCL, has broadened the therapeutic armamentarium for CTCL. Emerging therapeutic efforts are being focused on the development of multimodal immunotherapies employing agents that can induce a complete and durable clinical response through the activation of multiple immune cell populations, closely mimicking the natural sequence of events. Other potential treatment options such as monoclonal antibody therapy and immune

checkpoint blockade therapy are currently being investigated for their clinical efficacy. Investigations are also underway to test the potency of receptor inhibitors or anti-chemokine receptor antibodies to disrupt the diverse chemokine/chemokine receptor interactions within the tumor inflammatory TME. Benefitting from the clinical efficacy of approved and recommended Th1 cytokine IFN-α, restoration of Th1 responses through IFN-γ and IL-12 has emerged as an effective strategy to revive anti-tumor immune functions and, hence, achieve complete clinical response. TLR agonists, that can potently activate the innate immune response through the production of pro-inflammatory cytokines such as IFN-α, are being actively tested in clinical trials. Moreover, informed by the data obtained from comprehensive mapping of oncogenic pathways and their intersections within CTCL cells, several candidate agents are being subjected to efficacy screening against specific pathways. For example, the crucial role of the JAK/STAT pathway formed the basis of using a JAK inhibitor ruxolitinib in a phase II clinical trial against refractory or relapsed T cell lymphoma. It is also being preclinically assessed for its efficacy in combination formulations for clinical use in the treatment of advanced stage CTCL. Given the multilayer communication between signaling networks, combinatorial targeted drug regimens are expected to greatly enhance the therapeutic spectrum of CTCLs. Regardless, much work is still required for the clinical success of these therapies, given the heterogeneous nature of CTCLs that can significantly impact the clinical, cytotoxic, and immunotherapeutic responses. Understanding the sources, dynamics, and key spatiotemporal features of CTCL heterogeneity is, therefore, critical for the development of novel and effective therapeutics. In particular, given the heterogeneity and functional diversity of immune subsets within the CTCL TME, a holistic view of the immune atlas, including different immune signatures/contexture will help in prognosis prediction and guide immunotherapeutic decisions in CTCL patients. Moreover, since Th2-targeted therapies, chemokine and chemokine receptor blockers, as well as cell signaling inhibitors are in development or approved for other skin conditions or diseases, the precise characterization of the molecular pathways of all subtypes will help to optimize treatment for CTCL patients in the future. Above all this, considering the significant overlap in phenotypic features and immunologic pathogenesis between CTCL entities, their exact classification and clinicopathological correlation are important to attain correct diagnosis and treatment stratification for targeted therapies.

Data availability

No data was used for the research described in the article.

Author contribution

KP - conceptualization and writing, preparing illustrations and table; SK - table preparation and reviewing; AQK, FA - writing and reviewing; MA, JB, AA - Conceptualization and reviewing; MS - conceptualization and writing - reviewing and editing; SU- conceptualization, supervision, and writing - reviewing and editing.

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Declaration of Competing Interest

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References

[1] C. Cloninc, Cutaneous T-Cell Lymphoma, 2021 (Accessed 27 October 2021, https://my.clevelandclinic.org/health/diseases/17940-cutaneous-t-cell-lymphoma.
[2] L. Action, Skin (cutaneous) T-cell Lymphoma, 2021.
[3] I.V. Litvinov, M.T. Tetzlaff, E. Rahme, M.A. Jennings, D.R. Risser, P. Gangar, E. Netchiporouk, L. Moreau, V.G. Prieto, D. Sasseville, M. Duvic, Demographic patterns of cutaneous T-cell lymphoma incidence in Texas based on two different cancer registries, Cancer Med. 4 (9) (2015) 1440–1447.
[4] L.D. Wilson, G.A. Hinds, J.B. Yu, Age, race, sex, stage, and incidence of cutaneous lymphoma, Clin. Lymphoma Myeloma Leuk. 12 (5) (2012) 291–296.
[5] Q.A. Alsaleh, A. Nanda, H. Al-Ajmi, H. Al-Sabah, M. Elkashlan, S. Al-Shemmari, M.F. Demierre, Clinicoepidemiological features of mycosis fungoides in Kuwait, 1991-2006, Int. J. Dermatol. 49 (12) (2010) 1393–1398.
[6] G. Sun, C. Berthelot, Y. Li, D.A. Glass 2nd, D. George, A. Pandya, R. Kurzrock, M. Duvic, Poor prognosis in non-Caucasian patients with early-onset mycosis fungoides, J. Am. Acad. Dermatol. 60 (2) (2009) 231–235.
[7] R. Willemze, E.S. Jaffe, G. Burg, L. Cerroni, E. Berti, S.H. Swerdlow, E. Ralfkiaer, S. Chimenti, J.L. Diaz-Perez, L.M. Duncan, F. Grange, N.L. Harris, W. Kempf, H. Kerl, M. Kurrer, R. Knobler, N. Pimpinelli, C. Sander, M. Santucci, W. Sterry, M.H. Vermeer, J. Wechsler, S. Whittaker, C.J. Meijer, WHO-EORTC classification for cutaneous lymphomas, Blood 105 (10) (2005) 3768–3785.
[8] R. Willemze, L. Cerroni, W. Kempf, E. Berti, F. Facchetti, S.H. Swerdlow, E. S. Jaffe, The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas, Blood 133 (16) (2019) 1703–1714.
[9] S.H. Swerdlow, I.A.f.R.o. Cancer, W.H. Organization, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, International Agency for Research on Cancer, 2008.
[10] S.H. Swerdlow, E. Campo, S.A. Pileri, N.L. Harris, H. Stein, R. Siebert, R. Advani, M. Ghielmini, G.A. Salles, A.D. Zelenetz, E.S. Jaffe, The 2016 revision of the World Health Organization classification of lymphoid neoplasms, Blood 127 (20) (2016) 2375–2390.
[11] R. Willemze, CD30-negative cutaneous T-Cell lymphomas other than mycosis fungoides, Surg. Pathol. Clin. 7 (2) (2014) 229–252.
[12] F. Damasco, O.E. Akilov, Rare cutaneous T-Cell lymphomas, Hematol. Oncol. Clin. North Am. 33 (1) (2019) 135–148.
[13] C.A. Larocca, N.R. LeBoeuf, Overview of cutaneous T-Cell lymphomas, Hematol. Oncol. Clin. North Am. 33 (4) (2019) 669–686.
[14] C. Perez, R. Mondejar, N. Garcia-Diaz, L. Cereceda, A. Leon, S. Montes, C. Duran Vian, M.G. Perez Paredes, A. Gonzalez-Moran, V. Alegre de Miguel, J.M. Sanz Anquela, J. Frias, M.A. Limeres, L.M. Gonzalez, F. Martin Davila, M. Beltran, M. Mollejo, J.R. Mendez, M.A. Gonzalez, J. Gonzalez Garcia, R. Lopez, A. Gomez, F. Izquierdo, R. Ramos, C. Camacho, S.M. Rodriguez-Pinilla, N. Martinez, J. P. Vaque, P.L. Ortiz-Romero, M.A. Piris, Advanced-stage mycosis fungoides: role of the signal transducer and activator of transcription 3, nuclear factor-kappaB and nuclear factor of activated T cells pathways, Br. J. Dermatol. 182 (1) (2020) 147–155.
[15] G. Burg, Systemic involvement in mycosis fungoides, Clin. Dermatol. 33 (5) (2015) 563–571.
[16] E.J. Kim, S. Hess, S.K. Richardson, S. Newton, L.C. Showe, B.M. Benoit, R. Ubriani, C.C. Vittorio, J.M. Junkins-Hopkins, M. Wysocka, A.H. Rook, Immunopathogenesis and therapy of cutaneous T cell lymphoma, J. Clin. Invest. 115 (4) (2005) 798–812.
[17] J.J. Scarisbrick, P. Quaglino, H.M. Prince, E. Papadavid, E. Hodak, M. Bagot, O. Servitje, E. Berti, P. Ortiz-Romero, R. Stadler, A. Patsatsi, R. Knobler, E. Guenova, F. Child, S. Whittaker, V. Nikolaou, C. Tomasini, I. Amitay, H. Prag Naveh, C. Ram-Wolff, M. Battistella, S. Alberti-Violetti, R. Stranzenbach, V. Gargallo, C. Muniesa, T. Koletsa, C. Jonak, S. Porkert, C. Mitteldorf, T. Estrach, A. Combalia, M. Marschalko, J. Csomor, A. Szepesi, A. Cozzio, R. Dummer, N. Pimpinelli, V. Grandi, M. Beylot-Barry, A. Pham-Ledard, M. Wobser, E. Geissinger, U. Wehkamp, M. Weichenthal, R. Cowan, E. Parry, J. Harris, R. Wachsmuth, D. Turner, A. Bates, E. Healy, F. Trautinger, J. Latzka, J. Yoo, B. Vydianath, R. Amel-Kashipaz, L. Marinos, A. Oikonomidi, A. Stratigos, M. D. Vignon-Pennamen, M. Battistella, F. Climent, E. Gonzalez-Barca, E. Georgiou, R. Senetta, P. Zinzani, L. Vakeva, A. Ranki, A.M. Busschots, E. Hauben, A. Bervoets, A.J.F. Woei, R. Matin, G. Collins, S. Weatherhead, J. Frew, M. Bayne, G. Dunnill, P. McKay, A. Arumainathan, R. Azurdia, K. Benstead, R. Twigger, K. Rieger, R. Brown, J.A. Sanches, D. Miyashiro, O. Akilov, S. McCann, H. Sahi, F. M. Damasco, C. Querfeld, A. Folkes, C. Bur, C.D. Klemke, P. Enz, R. Pujol, K. Quint, L. Geskin, E. Hong, F. Evison, M. Vermeer, L. Cerroni, W. Kempf, Y. Kim, R. Willemze, The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients, Br. J. Dermatol. 181 (2) (2019) 350–357.
[18] P. Quaglino, N. Pimpinelli, E. Berti, P. Calzavara-Pinton, G. Alfonso Lombardo, S. Rupoli, M. Alaibac, U. Bottoni, A. Carbone, P. Fava, M. Fimiani, A.M. Mamusa, S. Titli, P.L. Zinzani, M.G. Bernengo, C. Gruppo Italiano Linfomi, Time course, clinical pathways, and long-term hazards risk trends of disease progression in patients with classic mycosis fungoides: a multicenter, retrospective follow-up study from the Italian Group of Cutaneous Lymphomas, Cancer 118 (23) (2012) 5830–5839.
[19] E.C. Vonderheid, M.G. Bernengo, G. Burg, M. Duvic, P. Heald, L. Laroche, E. Olsen, M. Pittelkow, R. Russell-Jones, M. Takigawa, R. Willemze, Iscl, Update on erythrodermic cutaneous T-cell lymphoma: report of the International Society for Cutaneous Lymphomas, J. Am. Acad. Dermatol. 46 (1) (2002) 95–106.

[20] A. Vakiti, S.A. Padala, D. Singh, Sezary Syndrome, StatPearls, Treasure Island (FL), 2021.
[21] A.C. Hristov, T. Tejasvi, R.A. Wilcox, Mycosis fungoides and Sezary syndrome: 2019 update on diagnosis, risk-stratification, and management, Am. J. Hematol. 94 (9) (2019) 1027–1041.
[22] J.J. Scarisbrick, Y.H. Kim, S.J. Whittaker, G.S. Wood, M.H. Vermeer, H.M. Prince, P. Quaglino, Prognostic factors, prognostic indices and staging in mycosis fungoides and Sezary syndrome: where are we now? Br. J. Dermatol. 170 (6) (2014) 1226–1236.
[23] N. Garcia-Diaz, M.A. Piris, P.L. Ortiz-Romero, J.P. Vaque, Mycosis fungoides and sezary syndrome: an integrative review of the pathophysiology, molecular drivers, and targeted therapy, Cancers (Basel) 13 (8) (2021).
[24] A. Iyer, D. Hennessey, S. O'Keefe, J. Patterson, W. Wang, G.K. Wong, R. Gniadecki, Branched evolution and genomic intratumor heterogeneity in the pathogenesis of cutaneous T-cell lymphoma, Blood Adv. 4 (11) (2020) 2489–2500.
[25] J. Choi, G. Goh, T. Walradt, B.S. Hong, C.G. Bunick, K. Chen, R.D. Bjornson, Y. Maman, T. Wang, J. Tordoff, K. Carlson, J.D. Overton, K.J. Liu, J.M. Lewis, L. Devine, L. Barbarotta, F.M. Foss, A. Subtil, E.C. Vonderheid, R.L. Edelson, D. G. Schatz, T.J. Boggon, M. Girardi, R.P. Lifton, Genomic landscape of cutaneous T cell lymphoma, Nat. Genet. 47 (9) (2015) 1011–1019.
[26] W.J. Woollard, V. Pullabhatla, A. Lorenc, V.M. Patel, R.M. Butler, A. Bayega, N. Begum, F. Bakr, K. Dedhia, J. Fisher, S. Aguilar-Duran, C. Flanagan, A. A. Ghasemi, R.M. Hoffmann, N. Castillo-Mosquera, E.A. Nuttall, A. Paul, C. A. Roberts, E.G. Solomonidis, R. Tarrant, A. Yoxall, C.Z. Beyers, S. Ferreira, I. Tosi, M.A. Simpson, E. de Rinaldis, T.J. Mitchell, S.J. Whittaker, Candidate driver genes involved in genome maintenance and DNA repair in Sezary syndrome, Blood 127 (26) (2016) 3387–3397.
[27] A. Ungewickell, A. Bhaduri, E. Rios, J. Reuter, C.S. Lee, A. Mah, A. Zehnder, R. Ohgami, S. Kulkarni, R. Armstrong, W.K. Weng, D. Gratzinger, M. Tavallaee, A. Rook, M. Snyder, Y. Kim, P.A. Khavari, Genomic analysis of mycosis fungoides and Sezary syndrome identifies recurrent alterations in TNFR2, Nat. Genet. 47 (9) (2015) 1056–1060.
[28] A.C. da Silva Almeida, F. Abate, H. Khiabanian, E. Martinez-Escala, J. Guitart, C. P. Tensen, M.H. Vermeer, R. Rabadan, A. Ferrando, T. Palomero, The mutational landscape of cutaneous T cell lymphoma and Sezary syndrome, Nat. Genet. 47 (12) (2015) 1465–1470.
[29] L. Wang, X. Ni, K.R. Covington, B.Y. Yang, J. Shiu, X. Zhang, L. Xi, Q. Meng, T. Langridge, J. Drummond, L.A. Donehower, H. Doddapaneni, D.M. Muzny, R. A. Gibbs, D.A. Wheeler, M. Duvic, Genomic profiling of Sezary syndrome identifies alterations of key T cell signaling and differentiation genes, Nat. Genet. 47 (12) (2015) 1426–1434.
[30] P. Zhang, M. Zhang, Epigenetics in the pathogenesis and treatment of cutaneous T-Cell lymphoma, Front. Oncol. 11 (2021), 663961.
[31] M.J. Kiel, A.A. Sahasrabuddhe, D.C.M. Rolland, T. Velusamy, F. Chung, M. Schaller, N.G. Bailey, B.L. Betz, R.N. Miranda, P. Porcu, J.C. Byrd, L. J. Medeiros, S.L. Kunkel, D.W. Bahler, M.S. Lim, K.S.J. Elenitoba-Johnson, Genomic analyses reveal recurrent mutations in epigenetic modifiers and the JAK-STAT pathway in Sezary syndrome, Nat. Commun. 6 (2015) 8470.
[32] L.Y. McGirt, P. Jia, D.A. Baerenwald, R.J. Duszynski, K.B. Dahlman, J.A. Zic, J. P. Zwerner, D. Hucks, U. Dave, Z. Zhao, C.M. Eischen, Whole-genome sequencing reveals oncogenic mutations in mycosis fungoides, Blood 126 (4) (2015) 508–519.
[33] J.J. Campbell, R.A. Clark, R. Watanabe, T.S. Kupper, Sezary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors, Blood 116 (5) (2010) 767–771.
[34] A.M. Gaydosik, D.S. Queen, M.H. Trager, O.E. Akilov, L.J. Geskin, P. Fuschiotti, Genome-wide transcriptome analysis of the STAT6-regulated genes in advanced-stage cutaneous T-cell lymphoma, Blood 136 (15) (2020) 1748–1759.
[35] T.B. Buus, A. Willerslev-Olsen, S. Fredholm, E. Blumel, C. Nastasi, M. Gluud, T. Hu, L.M. Lindahl, L. Iversen, H. Fogh, R. Gniadecki, I.V. Litvinov, J.L. Persson, C.M. Bonefeld, C. Geisler, J.P. Christensen, T. Krejsgaard, T. Litman, A. Woetmann, N. Odum, Single-cell heterogeneity in Sezary syndrome, Blood Adv. 2 (16) (2018) 2115–2126.
[36] R.M. Abraham, Q. Zhang, N. Odum, M.A. Wasik, The role of cytokine signaling in the pathogenesis of cutaneous T-cell lymphoma, Cancer Biol. Ther. 12 (12) (2011) 1019–1022.
[37] M. Roelens, M. Delord, C. Ram-Wolff, A. Marie-Cardine, A. Alberdi, G. Maki, L. Homyrda, A. Bensussan, M. Bagot, A. Toubert, H. Moins-Teisserenc, Circulating and skin-derived Sezary cells: clonal but with phenotypic plasticity, Blood 130 (12) (2017) 1468–1471.
[38] H. Moins-Teisserenc, M. Daubord, E. Clave, C. Douay, J. Felix, A. Marie-Cardine, C. Ram-Wolff, G. Maki, K. Beldjord, L. Homyrda, L. Michel, A. Bensussan, A. Toubert, M. Bagot, CD158k is a reliable marker for diagnosis of Sezary syndrome and reveals an unprecedented heterogeneity of circulating malignant cells, J. Invest. Dermatol. 135 (1) (2015) 247–257.
[39] P. Horna, L.C. Moscinski, L. Sokol, H. Shao, Naive/memory T-cell phenotypes in leukemic cutaneous T-cell lymphoma: putative cell of origin overlaps disease classification, Cytometry B Clin. Cytom. 96 (3) (2019) 234–241.
[40] A. Iyer, D. Hennessey, S. O'Keefe, J. Patterson, W. Wang, G.K. Wong, R. Gniadecki, Skin colonization by circulating neoplastic clones in cutaneous T-cell lymphoma, Blood 134 (18) (2019) 1517–1527.
[41] A. Hamrouni, H. Fogh, Z. Zak, N. Odum, R. Gniadecki, Clonotypic diversity of the T-cell receptor corroborates the immature precursor origin of cutaneous T-cell lymphoma, Clin. Cancer Res. 25 (10) (2019) 3104–3114.
[42] S. Poglio, M. Prochazkova-Carlotti, F. Cherrier, A. Gros, E. Laharanne, A. Pham-Ledard, M. Beylot-Barry, J.P. Merlio, Xenograft and cell culture models of Sezary syndrome reveal cell of origin diversity and subclonal heterogeneity, Leukemia 35 (6) (2021) 1696–1709.
[43] A.M. Gaydosik, T. Tabib, L.J. Geskin, C.A. Bayan, J.F. Conway, R. Lafyatis, P. Fuschiotti, Single-cell lymphocyte heterogeneity in advanced cutaneous T-cell lymphoma skin tumors, Clin. Cancer Res. 25 (14) (2019) 4443–4454.
[44] V. Stolearenco, M.R.J. Namini, S.S. Hasselager, M. Gluud, T.B. Buus, A. Willerslev-Olsen, N. Odum, T. Krejsgaard, Cellular interactions and inflammation in the pathogenesis of cutaneous T-Cell lymphoma, Front. Cell Dev. Biol. 8 (2020) 851.
[45] C. Thode, A. Woetmann, H.H. Wandall, M.C. Carlsson, K. Qvortrup, C.S. Kauczok, M. Wobser, A. Printzlau, N. Odum, S. Dabelsteen, Malignant T cells secrete galectins and induce epidermal hyperproliferation and disorganized stratification in a skin model of cutaneous T-cell lymphoma, J. Invest. Dermatol. 135 (1) (2015) 238–246.
[46] R.T. Hoppe, L.J. Medeiros, R.A. Warnke, G.S. Wood, CD8-positive tumor-infiltrating lymphocytes influence the long-term survival of patients with mycosis fungoides, J. Am. Acad. Dermatol. 32 (3) (1995) 448–453.
[47] H. Echchakir, M. Bagot, G. Dorothee, D. Martinvalet, S. Le Gouvello, L. Boumsell, S. Chouaib, A. Bensussan, F. Mami-Chouaib, Cutaneous T cell lymphoma reactive CD4+ cytotoxic T lymphocyte clones display a Th1 cytokine profile and use a fas-independent pathway for specific tumor cell lysis, J. Invest. Dermatol. 115 (1) (2000) 74–80.
[48] M. Bagot, H. Echchakir, F. Mami-Chouaib, M.H. Delfau-Larue, D. Charue, A. Bernheim, S. Chouaib, L. Boumsell, A. Bensussan, Isolation of tumor-specific cytotoxic CD4+ and CD4+CD8dim+ T-cell clones infiltrating a cutaneous T-cell lymphoma, Blood 91 (11) (1998) 4331–4341.
[49] D. Abeni, M. Frontani, F. Sampogna, F. Sera, S. Bolli, R. Corona, G. Baliva, G. Russo, Circulating CD8+ lymphocytes, white blood cells, and survival in patients with mycosis fungoides, Br. J. Dermatol. 153 (2) (2005) 324–330.
[50] M.H. Vermeer, R. van Doorn, D. Dukers, M.W. Bekkenk, C.J. Meijer, R. Willemze, CD8+ T cells in cutaneous T-cell lymphoma: expression of cytotoxic proteins, Fas Ligand, and killing inhibitory receptors and their relationship with clinical behavior, J. Clin. Oncol. 19 (23) (2001) 4322–4329.
[51] E.K. Yoo, M. Cassin, S.R. Lessin, A.H. Rook, Complete molecular remission during biologic response modifier therapy for Sezary syndrome is associated with enhanced helper T type 1 cytokine production and natural killer cell activity, J. Am. Acad. Dermatol. 45 (2) (2001) 208–216.
[52] P.I. Axelrod, B. Lorber, E.C. Vonderheid, Infections complicating mycosis fungoides and Sezary syndrome, JAMA 267 (10) (1992) 1354–1358.
[53] M.H. Goldgeier, S.R. Cohen, I.M. Braverman, K.S. Stenn, An unusual and fatal case of disseminated cutaneous herpes simplex. Infection in a patient with cutaneous T cell lymphoma (mycosis fungoides), J. Am. Acad. Dermatol. 4 (2) (1981) 176–180.
[54] M.A. Wasik, IL-13 as a novel growth factor in CTCL, Blood 125 (18) (2015) 2737–2738.
[55] K. Asadullah, W.D. Docke, A. Haeussler, W. Sterry, H.D. Volk, Progression of mycosis fungoides is associated with increasing cutaneous expression of interleukin-10 mRNA, J. Invest. Dermatol. 107 (6) (1996) 833–837.
[56] B.R. Vowels, S.R. Lessin, M. Cassin, C. Jaworsky, B. Benoit, J.T. Wolfe, A.H. Rook, Th2 cytokine mRNA expression in skin in cutaneous T-cell lymphoma, J. Invest. Dermatol. 103 (5) (1994) 669–673.
[57] T. Krejsgaard, L.M. Lindahl, N.P. Mongan, M.A. Wasik, I.V. Litvinov, L. Iversen, E. Langhoff, A. Woetmann, N. Odum, Malignant inflammation in cutaneous T-cell lymphoma-a hostile takeover, Semin. Immunopathol. 39 (3) (2017) 269–282.
[58] B. Rubio Gonzalez, J. Zain, S.T. Rosen, C. Querfeld, Tumor microenvironment in mycosis fungoides and Sezary syndrome, Curr. Opin. Oncol. 28 (1) (2016) 88–96.
[59] T. Miyagaki, M. Sugaya, Immunological milieu in mycosis fungoides and Sezary syndrome, J. Dermatol. 41 (1) (2014) 11–18.
[60] E. Guenova, R. Watanabe, J.E. Teague, J.A. Desimone, Y. Jiang, M. Dowlatshahi, C. Schlapbach, K. Schaekel, A.H. Rook, M. Tawa, D.C. Fisher, T.S. Kupper, R. A. Clark, TH2 cytokines from malignant cells suppress TH1 responses and enforce a global TH2 bias in leukemic cutaneous T-cell lymphoma, Clin. Cancer Res. 19 (14) (2013) 3755–3763.
[61] T. Miyagaki, M. Sugaya, H. Suga, M. Kamata, H. Ohmatsu, H. Fujita, Y. Asano, Y. Tada, T. Kadono, S. Sato, IL-22, but not IL-17, dominant environment in cutaneous T-cell lymphoma, Clin. Cancer Res. 17 (24) (2011) 7529–7538.
[62] Y. Iwakura, H. Ishigame, The IL-23/IL-17 axis in inflammation, J. Clin. Invest. 116 (5) (2006) 1218–1222.
[63] L.E. Harrington, P.R. Mangan, C.T. Weaver, Expanding the effector CD4 T-cell repertoire: the Th17 lineage, Curr. Opin. Immunol. 18 (3) (2006) 349–356.
[64] T. Krejsgaard, U. Ralfkiaer, E. Clasen-Linde, K.W. Eriksen, K.L. Kopp, C. M. Bonefeld, C. Geisler, S. Dabelsteen, M.A. Wasik, E. Ralfkiaer, A. Woetmann, N. Odum, Malignant cutaneous T-cell lymphoma cells express IL-17 utilizing the Jak3/Stat3 signaling pathway, J. Invest. Dermatol. 131 (6) (2011) 1331–1338.
[65] C.L. Berger, R. Tigelaar, J. Cohen, K. Mariwalla, J. Trinh, N. Wang, R.L. Edelson, Cutaneous T-cell lymphoma: malignant proliferation of T-regulatory cells, Blood 105 (4) (2005) 1640–1647.
[66] R. Dummer, P.W. Heald, F.O. Nestle, E. Ludwig, E. Laine, S. Hemmi, G. Burg, Sezary syndrome T-cell clones display T-helper 2 cytokines and express the accessory factor-1 (interferon-gamma receptor beta-chain), Blood 88 (4) (1996) 1383–1389.
[67] A.H. Rook, P. Heald, The immunopathogenesis of cutaneous T-cell lymphoma, Hematol. Oncol. Clin. North Am. 9 (5) (1995) 997–1010.

[68] C.L. Tendler, J.D. Burton, J. Jaffe, D. Danielpour, M. Charley, J.P. McCoy, M. R. Pittelkow, T.A. Waldmann, Abnormal cytokine expression in Sezary and adult T-cell leukemia cells correlates with the functional diversity between these T-cell malignancies, Cancer Res. 54 (16) (1994) 4430–4435.
[69] A.H. Rook, B.R. Vowels, C. Jaworsky, A. Singh, S.R. Lessin, The immunopathogenesis of cutaneous T-cell lymphoma. Abnormal cytokine production by Sezary T cells, Arch Dermatol 129 (4) (1993) 486–489.
[70] L.J. Geskin, S. Viragova, D.B. Stolz, P. Fuschiotti, Interleukin-13 is overexpressed in cutaneous T-cell lymphoma cells and regulates their proliferation, Blood 125 (18) (2015) 2798–2805.
[71] T. Krejsgaard, L.M. Gjerdrum, E. Ralfkiaer, B. Lauenborg, K.W. Eriksen, A. M. Mathiesen, L.F. Bovin, R. Gniadecki, C. Geisler, L.P. Ryder, Q. Zhang, M. A. Wasik, N. Odum, A. Woetmann, Malignant Tregs express low molecular splice forms of FOXP3 in Sezary syndrome, Leukemia 22 (12) (2008) 2230–2239.
[72] X. Wu, D.K. Hsu, K.H. Wang, Y. Huang, L. Mendoza, Y. Zhou, S.T. Hwang, IL-10 is overexpressed in human cutaneous T-cell lymphoma and is required for maximal tumor growth in a mouse model, Leuk. Lymphoma 60 (5) (2019) 1244–1252.
[73] R.A. Wilcox, D.A. Wada, S.C. Ziesmer, S.F. Elsawa, N.I. Comfere, A.B. Dietz, A. J. Novak, T.E. Witzig, A.L. Feldman, M.R. Pittelkow, S.M. Ansell, Monocytes promote tumor cell survival in T-cell lymphoproliferative disorders and are impaired in their ability to differentiate into mature dendritic cells, Blood 114 (14) (2009) 2936–2944.
[74] H. Ohmatsu, D. Humme, N. Gulati, J. Gonzalez, M. Mobs, M. Suarez-Farinas, I. Cardinale, H. Mitsui, E. Guttman-Yassky, W. Sterry, J.G. Krueger, IL32 is progressively expressed in mycosis fungoides independent of helper T-cell 2 and helper T-cell 9 polarization, Cancer Immunol. Res. 2 (9) (2014) 890–900.
[75] S.J. Mehdi, A. Moerman-Herzog, H.K. Wong, Normal and cancer fibroblasts differentially regulate TWIST1, TOX and cytokine gene expression in cutaneous T-cell lymphoma, BMC Cancer 21 (1) (2021) 492.
[76] H. Suga, M. Sugaya, T. Miyagaki, M. Kawaguchi, H. Fujita, Y. Asano, Y. Tada, T. Kadono, S. Sato, The role of IL-32 in cutaneous T-cell lymphoma, J. Invest. Dermatol. 134 (5) (2014) 1428–1435.
[77] A. Willerslev-Olsen, I.V. Litvinov, S.M. Fredholm, D.L. Petersen, N.A. Sibbesen, R. Gniadecki, Q. Zhang, C.M. Bonefeld, M.A. Wasik, C. Geisler, Y. Zhou, A. Woetmann, D. Sasseville, T. Krejsgaard, N. Odum, IL-15 and IL-17F are differentially regulated and expressed in mycosis fungoides (MF), Cell Cycle 13 (8) (2014) 1306–1312.
[78] S. Leroy, S. Dubois, I. Tenaud, N. Chebassier, A. Godard, Y. Jacques, B. Dreno, Interleukin-15 expression in cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome), Br. J. Dermatol. 144 (5) (2001) 1016–1023.
[79] K. Asadullah, A. Haeussler-Quade, S. Gellrich, S. Hanneken, T.E. Hansen-Hagge, W.D. Docke, H.D. Volk, W. Sterry, IL-15 and IL-16 overexpression in cutaneous T-cell lymphomas: stage-dependent increase in mycosis fungoides progression, Exp. Dermatol. 9 (4) (2000) 248–251.
[80] U. Dobbeling, R. Dummer, E. Laine, N. Potoczna, J.Z. Qin, G. Burg, Interleukin-15 is an autocrine/paracrine viability factor for cutaneous T-cell lymphoma cells, Blood 92 (1) (1998) 252–258.
[81] A. Mishra, K. La Perle, S. Kwiatkowski, L.A. Sullivan, G.H. Sams, J. Johns, D. P. Curphey, J. Wen, K. McConnell, J. Qi, H. Wong, G. Russo, J. Zhang, G. Marcucci, J.E. Bradner, P. Porcu, M.A. Caligiuri, Mechanism, Consequences, and Therapeutic Targeting of Abnormal IL15 Signaling in Cutaneous T-cell Lymphoma, Cancer Discov. 6 (9) (2016) 986–1005.
[82] M. Wysocka, N. Dawany, B. Benoit, A.V. Kossenkov, A.B. Troxel, J.M. Gelfand, M. K. Sell, L.C. Showe, A.H. Rook, Synergistic enhancement of cellular immune responses by the novel Toll receptor 7/8 agonist 3M-007 and interferon-gamma: implications for therapy of cutaneous T-cell lymphoma, Leuk. Lymphoma 52 (10) (2011) 1970–1979.
[83] M.L. Hansen, A. Woetmann, T. Krejsgaard, K.L. Kopp, R. Sokilde, T. Litman, P. T. Straten, C. Geisler, M.A. Wasik, N. Odum, K.W. Eriksen, IFN-alpha primes T- and NK-cells for IL-15-mediated signaling and cytotoxicity, Mol. Immunol. 48 (15–16) (2011) 2087–2093.
[84] M. Wysocka, B.M. Benoit, S. Newton, L. Azzoni, L.J. Montaner, A.H. Rook, Enhancement of the host immune responses in cutaneous T-cell lymphoma by CpG oligodeoxynucleotides and IL-15, Blood 104 (13) (2004) 4142–4149.
[85] J.Z. Qin, C.L. Zhang, J. Kamarashev, R. Dummer, G. Burg, U. Dobbeling, Interleukin-7 and interleukin-15 regulate the expression of the bcl-2 and c-myb genes in cutaneous T-cell lymphoma cells, Blood 98 (9) (2001) 2778–2783.
[86] M. Marzec, X. Liu, M. Kasprzycka, A. Witkiewicz, P.N. Raghunath, M. El-Salem, E. Robertson, N. Odum, M.A. Wasik, IL-2- and IL-15-induced activation of the rapamycin-sensitive mTORC1 pathway in malignant CD4+ T lymphocytes, Blood 111 (4) (2008) 2181–2189.
[87] T.A. Fehniger, M.A. Caligiuri, Interleukin 15: biology and relevance to human disease, Blood 97 (1) (2001) 14–32.
[88] B. Lauenborg, I.V. Litvinov, Y. Zhou, A. Willerslev-Olsen, C.M. Bonefeld, C. Nastasi, S. Fredholm, L.M. Lindahl, D. Sasseville, C. Geisler, M.M. Wasik, T. Krejsgaard, L.M.R. Gjerdrum, L. Iversen, N. Odum, A. Woetmann, Malignant T cells activate endothelial cells via IL-17 F, Blood Cancer J. 7 (7) (2017) e586.
[89] T. Krejsgaard, I.V. Litvinov, Y. Wang, L. Xia, A. Willerslev-Olsen, S.B. Koralov, K. L. Kopp, C.M. Bonefeld, M.A. Wasik, C. Geisler, A. Woetmann, Y. Zhou, D. Sasseville, N. Odum, Elucidating the role of interleukin-17F in cutaneous T-cell lymphoma, Blood 122 (6) (2013) 943–950.
[90] A.S. Chung, X. Wu, G. Zhuang, H. Ngu, I. Kasman, J. Zhang, J.M. Vernes, Z. Jiang, Y.G. Meng, F.V. Peale, W. Ouyang, N. Ferrara, An interleukin-17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy, Nat. Med. 19 (9) (2013) 1114–1123.
[91] M. Tuzova, J. Richmond, D. Wolpowitz, C. Curiel-Lewandrowski, K. Chaney, T. Kupper, W. Cruikshank, CCR4+T cell recruitment to the skin in mycosis fungoides: potential contributions by thymic stromal lymphopoietin and interleukin-16, Leuk. Lymphoma 56 (2) (2015) 440–449.
[92] M. Ito, K. Teshima, S. Ikeda, A. Kitadate, A. Watanabe, M. Nara, J. Yamashita, K. Ohshima, K. Sawada, H. Tagawa, MicroRNA-150 inhibits tumor invasion and metastasis by targeting the chemokine receptor CCR6, in advanced cutaneous T-cell lymphoma, Blood 123 (10) (2014) 1499–1511.
[93] S.R. Dillon, C. Sprecher, A. Hammond, J. Bilsborough, M. Rosenfeld-Franklin, S. R. Presnell, H.S. Haugen, M. Maurer, B. Harder, J. Johnston, S. Bort, S. Mudri, J. L. Kuijper, T. Bukowski, P. Shea, D.L. Dong, M. Dasovich, F.J. Grant, L. Lockwood, S.D. Levin, C. LeCiel, K. Waggie, H. Day, S. Topouzis, J. Kramer, R. Kuestner, Z. Chen, D. Foster, J. Parrish-Novak, J.A. Gross, Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice, Nat. Immunol. 5 (7) (2004) 752–760.
[94] J.M. Nemmer, M. Kuchner, A. Datsi, P. Olah, V. Julia, U. Raap, B. Homey, Interleukin-31 signaling bridges the gap between immune cells, the nervous system and epithelial tissues, Front. Med. (Lausanne) 8 (2021), 639097.
[95] I.S. Bagci, T. Ruzicka, IL-31: A new key player in dermatology and beyond, J. Allergy Clin. Immunol. 141 (3) (2018) 858–866.
[96] A. Datsi, M. Steinhoff, F. Ahmad, M. Alam, J. Buddenkotte, Interleukin-31: The "itchy" cytokine in inflammation and therapy, Allergy 76 (10) (2021) 2982–2997.
[97] A. Dreuw, S. Radtke, S. Pflanz, B.E. Lippok, P.C. Heinrich, H.M. Hermanns, Characterization of the signaling capacities of the novel gp130-like cytokine receptor, J. Biol. Chem. 279 (34) (2004) 36112–36120.
[98] M. Abreu, M. Miranda, M. Castro, I. Fernandes, R. Cabral, A.H. Santos, S. Fonseca, J. Rodrigues, M. Leander, C. Lau, I. Freitas, S. Coimbra, A. Santos-Silva, M. Lima, IL-31 and IL-8 in cutaneous T-Cell lymphoma: looking for their role in itch, Adv. Hematol. 2021 (2021), 5582581.
[99] E.M. Singer, D.B. Shin, L.A. Nattkemper, B.M. Benoit, R.S. Klein, C.A. Didigu, A. W. Loren, T. Dentchev, M. Wysocka, G. Yosipovitch, A.H. Rook, IL-31 is produced by the malignant T-cell population in cutaneous T-Cell lymphoma and correlates with CTCL pruritus, J. Invest. Dermatol. 133 (12) (2013) 2783–2785.
[100] S. van Santen, J.J. Out, W.H. Zoutman, K.D. Quint, R. Willemze, M.H. Vermeer, C. P. Tensen, Serum and cutaneous transcriptional expression levels of IL31 are minimal in cutaneous T cell lymphoma variants, Biochem. Biophys. Rep. 26 (2021), 101007.
[101] M. Wysocka, M.H. Zaki, L.E. French, J. Chehimi, M. Shapiro, S.E. Everetts, K. S. McGinnis, L. Montaner, A.H. Rook, Sezary syndrome patients demonstrate a defect in dendritic cell populations: effects of CD40 ligand and treatment with GM-CSF on dendritic cell numbers and the production of cytokines, Blood 100 (9) (2002) 3287–3294.
[102] B.R. Vowels, M. Cassin, E.C. Vonderheid, A.H. Rook, Aberrant cytokine production by Sezary syndrome patients: cytokine secretion pattern resembles murine Th2 cells, J. Invest. Dermatol. 99 (1) (1992) 90–94.
[103] A.H. Rook, M. Kubin, M. Cassin, E.C. Vonderheid, B.R. Vowels, J.T. Wolfe, S. F. Wolf, A. Singh, G. Trinchieri, S.R. Lessin, IL-12 reverses cytokine and immune abnormalities in Sezary syndrome, J. Immunol. 154 (3) (1995) 1491–1498.
[104] B.N. Lee, M. Duvic, C.K. Tang, C. Bueso-Ramos, Z. Estrov, J.M. Reuben, Dysregulated synthesis of intracellular type 1 and type 2 cytokines by T cells of patients with cutaneous T-cell lymphoma, Clin. Diagn. Lab. Immunol. 6 (1) (1999) 79–84.
[105] S.P. Robinson, S. Patterson, N. English, D. Davies, S.C. Knight, C.D. Reid, Human peripheral blood contains two distinct lineages of dendritic cells, Eur. J. Immunol. 29 (9) (1999) 2769–2778.
[106] B.F. Chong, A.J. Wilson, H.M. Gibson, M.S. Hafner, Y. Luo, C.J. Hedgcock, H. K. Wong, Immune function abnormalities in peripheral blood mononuclear cell cytokine expression differentiates stages of cutaneous T-cell lymphoma/mycosis fungoides, Clin. Cancer Res. 14 (3) (2008) 646–653.
[107] K.C. Manfrere, M.P. Torrealba, D.R. Miyashiro, L.M. Oliveira, G.C. de Carvalho, J. F. Lima, A.C. Branco, N.Z. Pereira, J. Pereira, J.A. Sanches Jr., M.N. Sato, Toll-like receptor agonists partially restore the production of pro-inflammatory cytokines and type I interferon in Sezary syndrome, Oncotarget 7 (46) (2016) 74592–74601.
[108] T. Miyagaki, M. Sugaya, H. Suga, H. Ohmatsu, H. Fujita, Y. Asano, Y. Tada, T. Kadono, S. Sato, Increased CCL18 expression in patients with cutaneous T-cell lymphoma: association with disease severity and prognosis, J. Eur. Acad. Dermatol. Venereol. 27 (1) (2013) e60–7.
[109] T. Miyagaki, M. Sugaya, H. Suga, S. Morimura, H. Ohmatsu, H. Fujita, Y. Asano, Y. Tada, T. Kadono, S. Sato, Low herpesvirus entry mediator (HVEM) expression on dermal fibroblasts contributes to a Th2-dominant microenvironment in advanced cutaneous T-cell lymphoma, J. Invest. Dermatol. 132 (4) (2012) 1280–1289.
[110] T. Miyagaki, M. Sugaya, H. Fujita, H. Ohmatsu, T. Kakinuma, T. Kadono, K. Tamaki, S. Sato, Eotaxins and CCR3 interaction regulates the Th2 environment of cutaneous T-cell lymphoma, J. Invest. Dermatol. 130 (9) (2010) 2304–2311.
[111] C.P. Tensen, M.H. Vermeer, P.M. van der Stoop, P. van Beek, R.J. Scheper, D. M. Boorsma, R. Willemze, Epidermal interferon-gamma inducible protein-10 (IP-10) and monokine induced by gamma-interferon (Mig) but not IL-8 mRNA expression is associated with epidermotropism in cutaneous T cell lymphomas, J. Invest. Dermatol. 111 (2) (1998) 222–226.
[112] D.N. Mauri, R. Ebner, R.I. Montgomery, K.D. Kochel, T.C. Cheung, G.L. Yu, S. Ruben, M. Murphy, R.J. Eisenberg, G.H. Cohen, P.G. Spear, C.F. Ware, LIGHT, a new member of the TNF superfamily, and lymphotoxin alpha are ligands for herpesvirus entry mediator, Immunity 8 (1) (1998) 21–30.

[113] Y. Morel, A. Truneh, R.W. Sweet, D. Olive, R.T. Costello, The TNF superfamily members LIGHT and CD154 (CD40 ligand) costimulate induction of dendritic cell maturation and elicit specific CTL activity, J. Immunol. 167 (5) (2001) 2479–2486.
[114] Y. Morel, J.M. Schiano de Colella, J. Harrop, K.C. Deen, S.D. Holmes, T. A. Wattam, S.S. Khandekar, A. Truneh, R.W. Sweet, J.A. Gastaut, D. Olive, R. T. Costello, Reciprocal expression of the TNF family receptor herpes virus entry mediator and its ligand LIGHT on activated T cells: LIGHT down-regulates its own receptor, J. Immunol. 165 (8) (2000) 4397–4404.
[115] F. Sallusto, C.R. Mackay, A. Lanzavecchia, Selective expression of the eotaxin receptor CCR3 by human T helper 2 cells, Science 277 (5334) (1997) 2005–2007.
[116] U. Forssmann, M. Uguccioni, P. Loetscher, C.A. Dahinden, H. Langen, M. Thelen, M. Baggiolini, Eotaxin-2, a novel CC chemokine that is selective for the chemokine receptor CCR3, and acts like eotaxin on human eosinophil and basophil leukocytes, J. Exp. Med. 185 (12) (1997) 2171–2176.
[117] K. Tanita, T. Fujimura, Y. Sato, C. Lyu, Y. Kambayashi, D. Ogata, S. Fukushima, A. Miyashita, H. Nakajima, M. Nakamura, A. Morita, S. Aiba, Bexarotene reduces production of CCL22 from tumor-associated macrophages in cutaneous T-Cell lymphoma, Front. Oncol. 9 (2019) 907.
[118] C. Gunther, N. Zimmermann, N. Berndt, M. Grosser, A. Stein, A. Koch, M. Meurer, Up-regulation of the chemokine CCL18 by macrophages is a potential immunomodulatory pathway in cutaneous T-cell lymphoma, Am. J. Pathol. 179 (3) (2011) 1434–1442.
[119] M. Vulcano, C. Albanesi, A. Stoppacciaro, R. Bagnati, G. D'Amico, S. Struyf, P. Transidico, R. Bonecchi, A. Del Prete, P. Allavena, L.P. Ruco, C. Chiabrando, G. Girolomoni, A. Mantovani, S. Sozzani, Dendritic cells as a major source of macrophage-derived chemokine/CCL22 in vitro and in vivo, Eur. J. Immunol. 31 (3) (2001) 812–822.
[120] P. Vieyra-Garcia, J.D. Crouch, J.T. O'Malley, E.W. Seger, C.H. Yang, J.E. Teague, A.M. Vromans, A. Gehad, T.S. Win, Z. Yu, E.L. Lowry, J.I. Na, A.H. Rook, P. Wolf, R.A. Clark, Benign T cells drive clinical skin inflammation in cutaneous T cell lymphoma, JCI Insight 4 (1) (2019).
[121] N. Takahashi, M. Sugaya, H. Suga, T. Oka, M. Kawaguchi, T. Miyagaki, H. Fujita, S. Sato, Thymic stromal chemokine TSLP acts through Th2 cytokine production to induce cutaneous T-cell lymphoma, Cancer Res. 76 (21) (2016) 6241–6252.
[122] S. Ebner, V.A. Nguyen, M. Forstner, Y.H. Wang, D. Wolfram, Y.J. Liu, N. Romani, Thymic stromal lymphopoietin converts human epidermal Langerhans cells into antigen-presenting cells that induce proallergic T cells, J. Allergy Clin. Immunol. 119 (4) (2007) 982–990.
[123] V. Soumelis, P.A. Reche, H. Kanzler, W. Yuan, G. Edward, B. Homey, M. Gilliet, S. Ho, S. Antonenko, A. Lauerma, K. Smith, D. Gorman, S. Zurawski, J. Abrams, S. Menon, T. McClanahan, R. de Waal-Malefyt Rd, F. Bazan, R.A. Kastelein, Y. J. Liu, Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP, Nat. Immunol. 3 (7) (2002) 673–680.
[124] M. Masuoka, H. Shiraishi, S. Ohta, S. Suzuki, K. Arima, S. Aoki, S. Toda, N. Inagaki, Y. Kurihara, S. Hayashida, S. Takeuchi, K. Koike, J. Ono, H. Noshiro, M. Furue, S.J. Conway, Y. Narisawa, K. Izuhara, Periostin promotes chronic allergic inflammation in response to Th2 cytokines, J. Clin. Invest. 122 (7) (2012) 2590–2600.
[125] T. Miyagaki, M. Sugaya, H. Fujita, H. Saeki, K. Tamaki, Increased serum thymic stromal lymphopoietin levels in patients with cutaneous T cell lymphoma, Clin. Exp. Dermatol. 34 (4) (2009) 539–540.
[126] W. Kempf, A.K. Zimmermann, C. Mitteldorf, Cutaneous lymphomas-An update 2019, Hematol. Oncol. 37 (Suppl 1) (2019) 43–47.
[127] J.P. Bottcher, E. Bonavita, P. Chakravarty, H. Blees, M. Cabeza-Cabrerizo, S. Sammicheli, N.C. Rogers, E. Sahai, S. Zelenay, C. Reis e Sousa, NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting Cancer immune control, Cell 172 (5) (2018) 1022–1037 e14.
[128] J. Jablonska, C.F. Wu, L. Andzinski, S. Leschner, S. Weiss, CXCR2-mediated tumor-associated neutrophil recruitment is regulated by IFN-beta, Int. J. Cancer 134 (6) (2014) 1346–1358.
[129] E. Schlecker, A. Stojanovic, C. Eisen, C. Quack, C.S. Falk, V. Umansky, A. Cerwenka, Tumor-infiltrating monocytic myeloid-derived suppressor cells mediate CCR5-dependent recruitment of regulatory T cells favoring tumor growth, J. Immunol. 189 (12) (2012) 5602–5611.
[130] X.S. Wu, A.S. Lonsdorf, S.T. Hwang, Cutaneous T-cell lymphoma: roles for chemokines and chemokine receptors, J. Invest. Dermatol. 129 (5) (2009) 1115–1119.
[131] S.K. Bromley, T.R. Mempel, A.D. Luster, Orchestrating the orchestrators: chemokines in control of T cell traffic, Nat. Immunol. 9 (9) (2008) 970–980.
[132] F. Sallusto, D. Lenig, C.R. Mackay, A. Lanzavecchia, Flexible programs of chemokine receptor expression on human polarized T helper 1 and 2 lymphocytes, J. Exp. Med. 187 (6) (1998) 875–883.
[133] T. Kakinuma, S.T. Hwang, Chemokines, chemokine receptors, and cancer metastasis, J. Leukoc. Biol. 79 (4) (2006) 639–651.
[134] Y.S. Lee CH, Pathophysiology of chemokines and chemokine receptors in dermatological science: a focus on psoriasis and cutaneous T-cell lymphoma, Dermatol. Sin. 30 (4) (2012).
[135] B. Homey, Chemokines and inflammatory skin diseases, Adv. Dermatol. 21 (2005) 251–277.
[136] Y. Reiss, A.E. Proudfoot, C.A. Power, J.J. Campbell, E.C. Butcher, CC chemokine receptor (CCR)4 and the CCR10 ligand cutaneous T cell-attracting chemokine (CTACK) in lymphocyte trafficking to inflamed skin, J. Exp. Med. 194 (10) (2001) 1541–1547.
[137] K. Ferenczi, R.C. Fuhlbrigge, J. Pinkus, G.S. Pinkus, T.S. Kupper, Increased CCR4 expression in cutaneous T cell lymphoma, J. Invest. Dermatol. 119 (6) (2002) 1405–1410.
[138] C.S. Wu, S.T. Wang, C.Y. Liao, M.T. Wu, Differential CCR4 expression and function in cutaneous T-cell lymphoma cell lines, Kaohsiung J. Med. Sci. 24 (11) (2008) 577–590.
[139] T. Kallinich, J.M. Muche, S. Qin, W. Sterry, H. Audring, R.A. Kroczek, Chemokine receptor expression on neoplastic and reactive T cells in the skin at different stages of mycosis fungoides, J. Invest. Dermatol. 121 (5) (2003) 1045–1052.
[140] T. Kakinuma, M. Sugaya, K. Nakamura, F. Kaneko, M. Wakugawa, K. Matsushima, K. Tamaki, Thymus and activation-regulated chemokine (TARC/CCL17) in mycosis fungoides: serum TARC levels reflect the disease activity of mycosis fungoides, J. Am. Acad. Dermatol. 48 (1) (2003) 23–30.
[141] D. Lu, M. Duvic, L.J. Medeiros, R. Luthra, D.M. Dorfman, D. Jones, The T-cell chemokine receptor CXCR3 is expressed highly in low-grade mycosis fungoides, Am. J. Clin. Pathol. 115 (3) (2001) 413–421.
[142] M.G. Narducci, E. Scala, A. Bresin, E. Caprini, M.C. Picchio, D. Remotti, G. Ragone, F. Nasorri, M. Frontani, D. Arcelli, S. Volinia, G.A. Lombardo, G. Baliva, M. Napolitano, G. Russo, Skin homing of Sezary cells involves SDF-1-CXCR4 signaling and down-regulation of CD26/dipeptidylpeptidase IV, Blood 107 (3) (2006) 1108–1115.
[143] A.M. Lambeir, P. Proost, C. Durinx, G. Bal, K. Senten, K. Augustyns, S. Scharpe, J. Van Damme, I. De Meester, Kinetic investigation of chemokine truncation by CD26/dipeptidyl peptidase IV reveals a striking selectivity within the chemokine family, J. Biol. Chem. 276 (32) (2001) 29839–29845.
[144] J. Maslowska, B. Swat, [Studies about the values of polycyclic aromatic hydrocarbons in oils used in production of plant protective agents], Rocz. Panstw. Zakl. Hig. 43 (2) (1992) 139–143.
[145] R. Forster, A. Schubel, D. Breitfeld, E. Kremmer, I. Renner-Muller, E. Wolf, M. Lipp, CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs, Cell 99 (1) (1999) 23–33.
[146] M. Sokolowska-Wojdylo, J. Wenzel, E. Gaffal, J. Lenz, P. Speuser, S. Erdmann, F. Abuzahra, E. Bowman, J. Roszkiewicz, T. Bieber, T. Tuting, Circulating clonal CLA(+) and CD4(+) T cells in Sezary syndrome express the skin-homing chemokine receptors CCR4 and CCR10 as well as the lymph node-homing chemokine receptor CCR7, Br. J. Dermatol. 152 (2) (2005) 258–264.
[147] N. Odum, Deregulated signalling and inflammation in cutaneous T-cell lymphoma, Br. J. Dermatol. 182 (1) (2020) 16–17.
[148] T.A. Waldmann, J. Chen, Disorders of the JAK/STAT pathway in t cell lymphoma pathogenesis: implications for immunotherapy, Annu. Rev. Immunol. 35 (2017) 533–550.
[149] V. Moresi, S. Adamo, L. Berghella, The JAK/STAT pathway in skeletal muscle pathophysiology, Front. Physiol. 10 (2019) 500.
[150] G.R. Stark, I.M. Kerr, B.R. Williams, R.H. Silverman, R.D. Schreiber, How cells respond to interferons, Annu. Rev. Biochem. 67 (1998) 227–264.
[151] J.E. Darnell Jr., STATs and gene regulation, Science 277 (5332) (1997) 1630–1635.
[152] J.S. Rawlings, K.M. Rosler, D.A. Harrison, The JAK/STAT signaling pathway, J. Cell. Sci. 117 (Pt 8) (2004) 1281–1283.
[153] D.S. Aaronson, C.M. Horvath, A road map for those who don't know JAK-STAT, Science 296 (5573) (2002) 1653–1655.
[154] T. Kisseleva, S. Bhattacharya, J. Braunstein, C.W. Schindler, Signaling through the JAK/STAT pathway, recent advances and future challenges, Gene 285 (1-2) (2002) 1–24.
[155] F. Seif, M. Khoshmirsafa, H. Aazami, M. Mohsenzadegan, G. Sedighi, M. Bahar, The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells, Cell Commun. Signal 15 (1) (2017) 23.
[156] E. Bousoik, H. Montazeri Aliabadi, "Do We Know Jack" About JAK? A Closer Look at JAK/STAT Signaling Pathway, Front. Oncol. 8 (2018) 287.
[157] B. Vogelstein, N. Papadopoulos, V.E. Velculescu, S. Zhou, L.A. Diaz Jr., K. W. Kinzler, Cancer genome landscapes, Science 339 (6127) (2013) 1546–1558.
[158] A. Seffens, A. Herrera, C. Tegla, T.B. Buus, K.B. Hymes, N. Odum, L.J. Geskin, S. B. Koralov, STAT3 dysregulation in mature t and NK cell lymphomas, Cancers (Basel) 11 (11) (2019).
[159] E. Netchiporouk, I.V. Litvinov, L. Moreau, M. Gilbert, D. Sasseville, M. Duvic, Deregulation in STAT signaling is important for cutaneous T-cell lymphoma (CTCL) pathogenesis and cancer progression, Cell Cycle 13 (21) (2014) 3331–3335.
[160] M.S. van Kester, J.J. Out-Luiting, P.A. von dem Borne, R. Willemze, C.P. Tensen, M.H. Vermeer, Cucurbitacin I inhibits Stat3 and induces apoptosis in Sezary cells, J. Invest. Dermatol. 128 (7) (2008) 1691–1695.
[161] M. Nielsen, C.G. Kaestel, K.W. Eriksen, A. Woetmann, T. Stokkedal, K. Kaltoft, C. Geisler, C. Ropke, N. Odum, Inhibition of constitutively activated Stat3 correlates with altered Bcl-2/Bax expression and induction of apoptosis in mycosis fungoides tumor cells, Leukemia 13 (5) (1999) 735–738.
[162] I.V. Litvinov, B. Cordeiro, S. Fredholm, N. Odum, H. Zargham, Y. Huang, Y. Zhou, K. Pehr, T.S. Kupper, A. Woetmann, D. Sasseville, Analysis of STAT4 expression in cutaneous T-cell lymphoma (CTCL) patients and patient-derived cell lines, Cell Cycle 13 (18) (2014) 2975–2982.
[163] L.C. Showe, F.E. Fox, D. Williams, K. Au, Z. Niu, A.H. Rook, Depressed IL-12-mediated signal transduction in T cells from patients with Sezary syndrome is associated with the absence of IL-12 receptor beta 2 mRNA and highly reduced levels of STAT4, J. Immunol. 163 (7) (1999) 4073–4079.

[164] V.E. Johnson, E.C. Vonderheid, A.D. Hess, C.M. Eischen, L.Y. McGirt, Genetic markers associated with progression in early mycosis fungoides, J. Eur. Acad. Dermatol. Venereol. 28 (11) (2014) 1431–1435.
[165] A.H. Rook, M. Kubin, F.E. Fox, Z. Niu, M. Cassin, B.R. Vowels, S.L. Gottleib, E. C. Vonderheid, S.R. Lessin, G. Trinchieri, The potential therapeutic role of interleukin-12 in cutaneous T-cell lymphoma, Ann. N. Y. Acad. Sci. 795 (1996) 310–318.
[166] A.H. Rook, G.S. Wood, E.K. Yoo, R. Elenitsas, D.M. Kao, M.L. Sherman, W. K. Witmer, K.A. Rockwell, R.B. Shane, S.R. Lessin, E.C. Vonderheid, Interleukin-12 therapy of cutaneous T-cell lymphoma induces lesion regression and cytotoxic T-cell responses, Blood 94 (3) (1999) 902–908.
[167] K.L. Kopp, U. Ralfkiaer, L.M. Gjerdrum, R. Helvad, I.H. Pedersen, T. Litman, L. Jonson, P.H. Hagedorn, T. Krejsgaard, R. Gniadecki, C.M. Bonefeld, L. Skov, C. Geisler, M.A. Wasik, E. Ralfkiaer, N. Odum, A. Woetmann, STAT5-mediated expression of oncogenic miR-155 in cutaneous T-cell lymphoma, Cell Cycle 12 (12) (2013) 1939–1947.
[168] V.H. Sommer, O.J. Clemmensen, O. Nielsen, M. Wasik, P. Lovato, C. Brender, K. W. Eriksen, A. Woetmann, C.G. Kaestel, M.H. Nissen, C. Ropke, S. Skov, N. Odum, In vivo activation of STAT3 in cutaneous T-cell lymphoma. Evidence for an antiapoptotic function of STAT3, Leukemia 18 (7) (2004) 1288–1295.
[169] J.Z. Qin, J. Kamarashev, C.L. Zhang, R. Dummer, G. Burg, U. Dobbeling, Constitutive and interleukin-7- and interleukin-15-stimulated DNA binding of STAT and novel factors in cutaneous T cell lymphoma cells, J. Invest. Dermatol. 117 (3) (2001) 583–589.
[170] L. van der Fits, J.J. Out-Luiting, M.A. van Leeuwen, J.N. Samsom, R. Willemze, C. P. Tensen, M.H. Vermeer, Autocrine IL-21 stimulation is involved in the maintenance of constitutive STAT3 activation in Sezary syndrome, J. Invest. Dermatol. 132 (2) (2012) 440–447.
[171] K.W. Eriksen, K. Kaltoft, G. Mikkelsen, M. Nielsen, Q. Zhang, C. Geisler, M. H. Nissen, C. Ropke, M.A. Wasik, N. Odum, Constitutive STAT3-activation in Sezary syndrome: tyrphostin AG490 inhibits STAT3-activation, interleukin-2 receptor expression and growth of leukemic Sezary cells, Leukemia 15 (5) (2001) 787–793.
[172] L. van der Fits, M.S. van Kester, Y. Qin, J.J. Out-Luiting, F. Smit, W.H. Zoutman, R. Willemze, C.P. Tensen, M.H. Vermeer, MicroRNA-21 expression in CD4+ T cells is regulated by STAT3 and is pathologically involved in Sezary syndrome, J. Invest. Dermatol. 131 (3) (2011) 762–768.
[173] T. Krejsgaard, C.S. Vetter-Kauczok, A. Woetmann, P. Lovato, T. Labuda, K. W. Eriksen, Q. Zhang, J.C. Becker, N. Odum, Jak3- and JNK-dependent vascular endothelial growth factor expression in cutaneous T-cell lymphoma, Leukemia 20 (10) (2006) 1759–1766.
[174] C. Brender, P. Lovato, V.H. Sommer, A. Woetmann, A.M. Mathiesen, C. Geisler, M. Wasik, N. Odum, Constitutive SOCS-3 expression protects T-cell lymphoma against growth inhibition by IFNalpha, Leukemia 19 (2) (2005) 209–213.
[175] C. Brender, M. Nielsen, K. Kaltoft, G. Mikkelsen, Q. Zhang, M. Wasik, N. Billestrup, N. Odum, STAT3-mediated constitutive expression of SOCS-3 in cutaneous T-cell lymphoma, Blood 97 (4) (2001) 1056–1062.
[176] S. Ikeda, A. Kitadate, M. Ito, F. Abe, M. Nara, A. Watanabe, N. Takahashi, T. Miyagaki, M. Sugaya, H. Tagawa, Disruption of CCL20-CCR6 interaction inhibits metastasis of advanced cutaneous T-cell lymphoma, Oncotarget 7 (12) (2016) 13563–13574.
[177] L.M. Lindahl, S. Fredholm, C. Joseph, B.S. Nielsen, L. Jonson, A. Willerslev-Olsen, M. Gluud, E. Blumel, D.L. Petersen, N. Sibbesen, T. Hu, C. Nastasi, T. Krejsgaard, D. Jaehger, J.L. Persson, N. Mongan, M.A. Wasik, I.V. Litvinov, D. Sasseville, S. B. Koralov, C.M. Bonefeld, C. Geisler, A. Woetmann, E. Ralfkiaer, L. Iversen, N. Odum, STAT5 induces miR-21 expression in cutaneous T cell lymphoma, Oncotarget 7 (29) (2016) 45730–45744.
[178] N.A. Sibbesen, K.L. Kopp, I.V. Litvinov, L. Jonson, A. Willerslev-Olsen, S. Fredholm, D.L. Petersen, C. Nastasi, T. Krejsgaard, L.M. Lindahl, R. Gniadecki, N.P. Mongan, D. Sasseville, M.A. Wasik, L. Iversen, C.M. Bonefeld, C. Geisler, A. Woetmann, N. Odum, Jak3, STAT3, and STAT5 inhibit expression of miR-22, a novel tumor suppressor microRNA, in cutaneous T-Cell lymphoma, Oncotarget 6 (24) (2015) 20555–20569.
[179] A. Majoros, E. Platanitis, E. Kernbauer-Holzl, F. Rosebrock, M. Muller, T. Decker, Canonical and non-canonical aspects of JAK-STAT signaling: lessons from interferons for cytokine responses, Front. Immunol. 8 (2017) 29.
[180] W.X. Li, Canonical and non-canonical JAK-STAT signaling, Trends Cell Biol. 18 (11) (2008) 545–551.
[181] C.K. Vadivel, M. Gluud, S. Torres-Rusillo, L. Boding, A. Willerslev-Olsen, T. B. Buus, T.K. Nielsen, J.L. Persson, C.M. Bonefeld, C. Geisler, T. Krejsgaard, A. T. Fuglsang, N. Odum, A. Woetmann, JAK3 is expressed in the nucleus of malignant t cells in cutaneous t cell lymphoma (CTCL), Cancers (Basel) 13 (2) (2021).
[182] Q. Zhang, H.Y. Wang, A. Woetmann, P.N. Raghunath, N. Odum, M.A. Wasik, STAT3 induces transcription of the DNA methyltransferase 1 gene (DNMT1) in malignant T lymphocytes, Blood 108 (3) (2006) 1058–1064.
[183] E. Hervouet, P. Peixoto, R. Delage-Mourroux, M. Boyer-Guittaut, P.F. Cartron, Specific or not specific recruitment of DNMTs for DNA methylation, an epigenetic dilemma, Clin. Epigenetics 10 (2018) 17.
[184] Q. Zhang, P.N. Raghunath, E. Vonderheid, N. Odum, M.A. Wasik, Lack of phosphotyrosine phosphatase SHP-1 expression in malignant T-cell lymphoma cells results from methylation of the SHP-1 promoter, Am. J. Pathol. 157 (4) (2000) 1137–1146.
[185] A. Willerslev-Olsen, T. Krejsgaard, L.M. Lindahl, I.V. Litvinov, S. Fredholm, D. L. Petersen, C. Nastasi, R. Gniadecki, N.P. Mongan, D. Sasseville, M.A. Wasik, C. M. Bonefeld, C. Geisler, A. Woetmann, L. Iversen, M. Kilian, S.B. Koralov, N. Odum, Staphylococcal enterotoxin A (SEA) stimulates STAT3 activation and IL-17 expression in cutaneous T-cell lymphoma, Blood 127 (10) (2016) 1287–1296.
[186] S. Ehrentraut, B. Schneider, S. Nagel, C. Pommerenke, H. Quentmeier, R. Geffers, M. Feist, M. Kaufmann, C. Meyer, M.E. Kadin, H.G. Drexler, R.A. MacLeod, Th17 cytokine differentiation and loss of plasticity after SOCS1 inactivation in a cutaneous T-cell lymphoma, Oncotarget 7 (23) (2016) 34201–34216.
[187] C. Perez, J. Gonzalez-Rincon, A. Onaindia, C. Almaraz, N. Garcia-Diaz, H. Pisonero, S. Curiel-Olmo, S. Gomez, L. Cereceda, R. Madureira, M. Hospital, D. Suarez-Massa, J.L. Rodriguez-Peralto, C. Postigo, A. Leon-Castillo, C. Gonzalez-Vela, N. Martinez, P. Ortiz-Romero, M. Sanchez-Beato, M.A. Piris, J.P. Vaque, Mutated JAK kinases and deregulated STAT activity are potential therapeutic targets in cutaneous T-cell lymphoma, Haematologica 100 (11) (2015) e450–3.
[188] I. Vivanco, C.L. Sawyers, The phosphatidylinositol 3-Kinase AKT pathway in human cancer, Nat. Rev. Cancer 2 (7) (2002) 489–501.
[189] M. Kremer, K. Sliva, C.D. Klemke, B.S. Schnierle, Cutaneous T-cell lymphoma cells are sensitive to rapamycin, Exp. Dermatol. 19 (9) (2010) 800–805.
[190] M. Tesio, A. Trinquand, E. Macintyre, V. Asnafi, Oncogenic PTEN functions and models in T-cell malignancies, Oncogene 35 (30) (2016) 3887–3896.
[191] W.L. Zhao, Targeted therapy in T-cell malignancies: dysregulation of the cellular signaling pathways, Leukemia 24 (1) (2010) 13–21.
[192] C. Cristofoletti, A. Bresin, M. Picozza, M.C. Picchio, F. Monzo, M. Helmer Citterich, F. Passarelli, A. Frezzolini, E. Scala, A. Monopoli, M. Cantonetti, R. Benucci, S. D'Atri, E. Caprini, G. Russo, M.G. Narducci, Blood and skin-derived Sezary cells: differences in proliferation-index, activation of PI3K/AKT/mTORC1 pathway and its prognostic relevance, Leukemia 33 (5) (2019) 1231–1242.
[193] E. Caprini, C. Cristofoletti, D. Arcelli, P. Fadda, M.H. Citterich, F. Sampogna, A. Magrelli, F. Censi, P. Torreri, M. Frontani, E. Scala, M.C. Picchio, P. Temperani, A. Monopoli, G.A. Lombardo, D. Taruscio, M.G. Narducci, G. Russo, Identification of key regions and genes important in the pathogenesis of sezary syndrome by combining genomic and expression microarrays, Cancer Res. 69 (21) (2009) 8438–8446.
[194] M. Pulitzer, P.L. Myskowski, S.M. Horwitz, C. Querfeld, B. Connolly, J. Li, R. Murali, Mycosis fungoides with large cell transformation: clinicopathological features and prognostic factors, Pathology 46 (7) (2014) 610–616.
[195] K.E. Salhany, J.B. Cousar, J.P. Greer, T.T. Casey, J.P. Fields, R.D. Collins, Transformation of cutaneous T cell lymphoma to large cell lymphoma, A clinicopathologic and immunologic study, Am J Pathol 132 (2) (1988) 265–277.
[196] L. Borsig, M.J. Wolf, M. Roblek, A. Lorentzen, M. Heikenwalder, Inflammatory chemokines and metastasis–tracing the accessory, Oncogene 33 (25) (2014) 3217–3224.
[197] R. Munk, P. Ghosh, M.C. Ghosh, T. Saito, M. Xu, A. Carter, F. Indig, D.D. Taub, D. L. Longo, Involvement of mTOR in CXCL12 mediated T cell signaling and migration, PLoS One 6 (9) (2011), e24667.
[198] G. Levidou, M. Siakantaris, T. Papadaki, E. Papadavid, T.P. Vassilakopoulos, M. K. Angelopoulou, L. Marinos, V. Nikolaou, A. Economidi, C. Antoniou, E. Patsouris, P. Korkolopoulou, A comprehensive immunohistochemical approach of AKT/mTOR pathway and p-STAT3 in mycosis fungoides, J. Am. Acad. Dermatol. 69 (3) (2013) 375–384.
[199] B. Fine, C. Hodakoski, S. Koujak, T. Su, L.H. Saal, M. Maurer, B. Hopkins, M. Keniry, M.L. Sulis, S. Mense, H. Hibshoosh, R. Parsons, Activation of the PI3K pathway in cancer through inhibition of PTEN by exchange factor P-REX2a, Science 325 (5945) (2009) 1261–1265.
[200] M.H. Yang, C.H. Yen, Y.F. Chen, C.C. Fang, C.H. Li, K.J. Lee, Y.H. Lin, C.H. Weng, T.T. Liu, S.F. Huang, B.T. Teh, Y.A. Chen, Somatic mutations of PREX2 gene in patients with hepatocellular carcinoma, Sci. Rep. 9 (1) (2019) 2552.
[201] E. Papadavid, P. Korkolopoulou, G. Levidou, A.A. Saetta, T. Papadaki, M. Siakantaris, V. Nikolaou, A. Oikonomidi, I. Chatziandreou, L. Marinos, A. Kolialexi, A. Stratigos, D. Rigopoulos, A. Psyrri, E. Patsouris, C. Antoniou, In situ assessment of PI3K and PTEN alterations in mycosis fungoides: correlation with clinicopathological features, Exp. Dermatol. 23 (12) (2014) 931–933.
[202] V. Manfe, E. Biskup, A. Rosbjerg, M. Kamstrup, A.G. Skov, C.M. Lerche, B. T. Lauenborg, N. Odum, R. Gniadecki, miR-122 regulates p53/Akt signalling and the chemotherapy-induced apoptosis in cutaneous T-cell lymphoma, PLoS One 7 (1) (2012), e29541.
[203] T. Liu, L. Zhang, D. Joo, S.C. Sun, NF-kappaB signaling in inflammation, Signal Transduct. Target. Ther. 2 (2017).
[204] H. Guo, J.B. Callaway, J.P. Ting, Inflammasomes: mechanism of action, role in disease, and therapeutics, Nat. Med. 21 (7) (2015) 677–687.
[205] H. Kumar, T. Kawai, S. Akira, Pathogen recognition by the innate immune system, Int. Rev. Immunol. 30 (1) (2011) 16–34.
[206] J. Zhu, H. Yamane, W.E. Paul, Differentiation of effector CD4 T cell populations (*), Annu. Rev. Immunol. 28 (2010) 445–489.
[207] M. Schmidt-Supprian, J. Tian, E.P. Grant, M. Pasparakis, R. Maehr, H. Ovaa, H. L. Ploegh, A.J. Coyle, K. Rajewsky, Differential dependence of CD4+CD25+ regulatory and natural killer-like T cells on signals leading to NF-kappaB activation, Proc. Natl. Acad. Sci. U. S. A. 101 (13) (2004) 4566–4571.
[208] T.P. Chang, I. Vancurova, NFkappaB function and regulation in cutaneous T-cell lymphoma, Am. J. Cancer Res. 3 (5) (2013) 433–445.
[209] A. Oeckinghaus, S. Ghosh, The NF-kappaB family of transcription factors and its regulation, Cold Spring Harb. Perspect. Biol. 1 (4) (2009), a000034.
[210] S.T. Smale, Dimer-specific regulatory mechanisms within the NF-kappaB family of transcription factors, Immunol. Rev. 246 (1) (2012) 193–204.
[211] S. Vallabhapurapu, M. Karin, Regulation and function of NF-kappaB transcription factors in the immune system, Annu. Rev. Immunol. 27 (2009) 693–733.

[212] A. Sors, F. Jean-Louis, C. Pellet, L. Laroche, L. Dubertret, G. Courtois, H. Bachelez, L. Michel, Down-regulating constitutive activation of the NF-kappaB canonical pathway overcomes the resistance of cutaneous T-cell lymphoma to apoptosis, Blood 107 (6) (2006) 2354–2363.
[213] M.K. Kiessling, C.D. Klemke, M.M. Kaminski, I.E. Galani, P.H. Krammer, K. Gulow, Inhibition of constitutively activated nuclear factor-kappaB induces reactive oxygen species- and iron-dependent cell death in cutaneous T-cell lymphoma, Cancer Res. 69 (6) (2009) 2365–2374.
[214] M.L. Cho, J.W. Kang, Y.M. Moon, H.J. Nam, J.Y. Jhun, S.B. Heo, H.T. Jin, S. Y. Min, J.H. Ju, K.S. Park, Y.G. Cho, C.H. Yoon, S.H. Park, Y.C. Sung, H.Y. Kim, STAT3 and NF-kappaB signal pathway is required for IL-23-mediated IL-17 production in spontaneous arthritis animal model IL-1 receptor antagonist-deficient mice, J. Immunol. 176 (9) (2006) 5652–5661.
[215] D.K. Giri, B.B. Aggarwal, Constitutive activation of NF-kappaB causes resistance to apoptosis in human cutaneous T cell lymphoma HuT-78 cells. Autocrine role of tumor necrosis factor and reactive oxygen intermediates, J. Biol. Chem. 273 (22) (1998) 14008–14014.
[216] J. Wu, G.S. Wood, Reduction of Fas/CD95 promoter methylation, upregulation of Fas protein, and enhancement of sensitivity to apoptosis in cutaneous T-cell lymphoma, Arch. Dermatol. 147 (4) (2011) 443–449.
[217] E. Volpe, M. Sambucci, L. Battistini, G. Borsellino, Fas-Fas Ligand, Checkpoint of t cell functions in multiple sclerosis, Front. Immunol. 7 (2016) 382.
[218] J.E. Castro, J.A. Listman, B.A. Jacobson, Y. Wang, P.A. Lopez, S. Ju, P.W. Finn, D. L. Perkins, Fas modulation of apoptosis during negative selection of thymocytes, Immunity 5 (6) (1996) 617–627.
[219] P. Bouillet, L.A. O'Reilly, CD95, BIM and T cell homeostasis, Nat. Rev. Immunol. 9 (7) (2009) 514–519.
[220] J. Wu, M. Nihal, J. Siddiqui, E.C. Vonderheid, G.S. Wood, Low FAS/CD95 expression by CTCL correlates with reduced sensitivity to apoptosis that can be restored by FAS upregulation, J. Invest. Dermatol. 129 (5) (2009) 1165–1173.
[221] J. Wu, J. Siddiqui, M. Nihal, E.C. Vonderheid, G.S. Wood, Structural alterations of the FAS gene in cutaneous T-cell lymphoma (CTCL), Arch. Biochem. Biophys. 508 (2) (2011) 185–191.
[222] S. Cao, X. Zhang, J.P. Edwards, D.M. Mosser, NF-kappaB1 (p50) homodimers differentially regulate pro- and anti-inflammatory cytokines in macrophages, J. Biol. Chem. 281 (36) (2006) 26041–26050.
[223] N. Mori, D. Prager, Activation of the interleukin-10 gene in the human T lymphoma line HuT 78: identification and characterization of NF-kappa B binding sites in the regulatory region of the interleukin-10 gene, Eur. J. Haematol. 59 (3) (1997) 162–170.
[224] A. Neri, N.S. Fracchiolla, A. Migliazza, D. Trecca, L. Lombardi, The involvement of the candidate proto-oncogene NFKB2/lyt-10 in lymphoid malignancies, Leuk. Lymphoma 23 (1–2) (1996) 43–48.
[225] D. Wang, Y. You, S.M. Case, L.M. McAllister-Lucas, L. Wang, P.S. DiStefano, G. Nunez, J. Bertin, X. Lin, A requirement for CARMA1 in TCR-induced NF-kappa B activation, Nat. Immunol. 3 (9) (2002) 830–835.
[226] F.C. Braun, P. Grabarczyk, M. Mobs, F.K. Braun, J. Eberle, M. Beyer, W. Sterry, F. Busse, J. Schroder, M. Delin, G.K. Przybylski, C.A. Schmidt, Tumor suppressor TNFAIP3 (A20) is frequently deleted in Sezary syndrome, Leukemia 25 (9) (2011) 1494–1501.
[227] L. Vereecke, R. Beyaert, G. Van Loo, The ubiquitin-editing enzyme A20 (TNFAIP3) is a central regulator of immunopathology, Trends Immunol. 30 (8) (2009) 383–391.
[228] F. Gallardo, J. Bertran, E. Lopez-Arribillaga, J. Gonzalez, S. Menendez, I. Sanchez, L. Colomo, M. Iglesias, M. Garrido, L.F. Santamaria-Babi, F. Torres, R.M. Pujol, A. Bigas, L. Espinosa, Novel phosphorylated TAK1 species with functional impact on NF-kappaB and beta-catenin signaling in human Cutaneous T-cell lymphoma, Leukemia 32 (10) (2018) 2211–2223.
[229] J. Park, J. Yang, A.T. Wenzel, A. Ramachandran, W.J. Lee, J.C. Daniels, J. Kim, E. Martinez-Escala, N. Amankulor, B. Pro, J. Guitart, M.L. Mendillo, J.N. Savas, T. J. Boggon, J. Choi, Genomic analysis of 220 CTCLs identifies a novel recurrent gain-of-function alteration in RLTPR (p.Q575E), Blood 130 (12) (2017) 1430–1440.
[230] R. Roncagalli, M. Cucchetti, N. Jarmuzynski, C. Gregoire, E. Bergot, S. Audebert, E. Baudelet, M.G. Menoita, A. Joachim, S. Durand, M. Suchanek, F. Fiore, L. Zhang, Y. Liang, L. Camoin, M. Malissen, B. Malissen, The scaffolding function of the RLTPR protein explains its essential role for CD28 co-stimulation in mouse and human T cells, J. Exp. Med. 213 (11) (2016) 2437–2457.
[231] Y.J. Guo, W.W. Pan, S.B. Liu, Z.F. Shen, Y. Xu, L.L. Hu, ERK/MAPK signalling pathway and tumorigenesis, Exp. Ther. Med. 19 (3) (2020) 1997–2007.
[232] J.M. Kyriakis, J. Avruch, Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation, Physiol. Rev. 81 (2) (2001) 807–869.
[233] S.F. Krens, H.P. Spaink, B.E. Snaar-Jagalska, Functions of the MAPK family in vertebrate-development, FEBS Lett. 580 (21) (2006) 4984–4990.
[234] Z. Chen, T.B. Gibson, F. Robinson, L. Silvestro, G. Pearson, B. Xu, A. Wright, C. Vanderbilt, M.H. Cobb, MAP kinases, Chem. Rev. 101 (8) (2001) 2449–2476.
[235] H.J. Schaeffer, M.J. Weber, Mitogen-activated protein kinases: specific messages from ubiquitous messengers, Mol. Cell. Biol. 19 (4) (1999) 2435–2444.
[236] A.S. Dhillon, S. Hagan, O. Rath, W. Kolch, MAP kinase signalling pathways in cancer, Oncogene 26 (22) (2007) 3279–3290.
[237] M.K. Kiessling, P.A. Oberholzer, C. Mondal, M.B. Karpova, M.C. Zipser, W.M. Lin, M. Girardi, L.E. Macconaill, S.M. Kehoe, C. Hatton, L.E. French, L.A. Garraway, G. Polier, D. Suss, C.D. Klemke, P.H. Krammer, K. Gulow, R. Dummer, High-throughput mutation profiling of CTCL samples reveals KRAS and NRAS mutations sensitizing tumors toward inhibition of the RAS/RAF/MEK signaling cascade, Blood 117 (8) (2011) 2433–2440.
[238] B.S. Braun, K. Shannon, Targeting Ras in myeloid leukemias, Clin. Cancer Res. 14 (8) (2008) 2249–2252.
[239] K.V. Argyropoulos, M. Pulitzer, F. Maura, A. Mohanty, P. Mondello, S.M. Horwitz, P. Myskowski, A. Moskowitz, A. Dogan, C. Querfeld, F. Rapaport, M. Siakantaris, P.C. Louis, N. Galasso, M.R.M. van den Brink, M.L. Palomba, Targeted genomic analysis of cutaneous T cell lymphomas identifies a subset with aggressive clinicopathological features, Blood Cancer J. 10 (11) (2020) 116.
[240] M. Bliss-Moreau, C. Coarfa, P.H. Gunaratne, J. Guitart, N.L. Krett, S.T. Rosen, Identification of p38beta as a therapeutic target for the treatment of Sezary syndrome, J. Invest. Dermatol. 135 (2) (2015) 599–608.
[241] A.R. Chakraborty, R.W. Robey, V.L. Luchenko, Z. Zhan, R.L. Piekarz, J.P. Gillet, A. V. Kossenkov, J. Wilkerson, L.C. Showe, M.M. Gottesman, N.L. Collie, S.E. Bates, MAPK pathway activation leads to Bim loss and histone deacetylase inhibitor resistance: rationale to combine romidepsin with an MEK inhibitor, Blood 121 (20) (2013) 4115–4125.
[242] W. Kempf, C. Mitteldorf, Cutaneous T-cell lymphomas-An update 2021, Hematol. Oncol. 39 (Suppl 1) (2021) 46–51.
[243] M.I.B. Malveira, G. Pascoal, S.B.L. Gamonal, M. Castanon, Folliculotropic mycosis fungoides: challenging clinical, histopathological and immunohistochemical diagnosis, An. Bras. Dermatol. 92 (5 Suppl 1) (2017) 73–75.
[244] A. Shah, A. Safaya, Granulomatous slack skin disease: a review, in comparison with mycosis fungoides, J. Eur. Acad. Dermatol. Venereol. 26 (12) (2012) 1472–1478.
[245] C.D. Klemke, N. Booken, C. Weiss, J.P. Nicolay, S. Goerdt, M. Felcht, C. Geraud, W. Kempf, C. Assaf, N. Ortonne, M. Battistella, M. Bagot, R. Knobler, P. Quaglino, B. Arheiliger, M. Santucci, P. Jansen, M.H. Vermeer, R. Willemze, Histopathological and immunophenotypical criteria for the diagnosis of Sezary syndrome in differentiation from other erythrodermic skin diseases: a European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force Study of 97 cases, Br. J. Dermatol. 173 (1) (2015) 93–105.
[246] Y. Tokura, Y. Sawada, T. Shimauchi, Skin manifestations of adult T-cell leukemia/lymphoma: clinical, cytological and immunological features, J. Dermatol. 41 (1) (2014) 19–25.
[247] A. Khader, M. Shaan, S. Sasidharanpillai, J. Pakran, U. Rajan, Adult T-cell leukemia/lymphoma: a retroviral malady, Indian J. Dermatol. 57 (3) (2012) 219–221.
[248] W. Kempf, K. Kerl, C. Mitteldorf, Cutaneous CD30-positive T-cell lymphoproliferative disorders-clinical and histopathologic features, differential diagnosis, and treatment, Semin. Cutan. Med. Surg. 37 (1) (2018) 24–29.
[249] S.R. Musick, D.T. Lynch, Subcutaneous Panniculitis Like T-cell Lymphoma, StatPearls, Treasure Island (FL), 2021.
[250] R.H. Gormley, S.D. Hess, D. Anand, J. Junkins-Hopkins, A.H. Rook, E.J. Kim, Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma, J. Am. Acad. Dermatol. 62 (2) (2010) 300–307.
[251] M. Maurelli, C. Colato, P. Gisondi, G. Girolomoni, Primary cutaneous CD4(+) Small/Medium pleomorphic T-Cell lymphoproliferative disorder: a case series, J. Cutan. Med. Surg. 21 (6) (2017) 502–506.
[252] V.M. Hathuc, A.C. Hristov, L.B. Smith, Primary cutaneous acral CD8(+) T-Cell lymphoma, Arch. Pathol. Lab. Med. 141 (11) (2017) 1469–1475.
[253] H. Gill, R.H. Liang, E. Tse, Extranodal natural-killer/t-cell lymphoma, nasal type, Adv. Hematol. 2010 (2010), 627401.
[254] M. Marzec, K. Halasa, M. Kasprzycka, M. Wysocka, X. Liu, J.W. Tobias, D. Baldwin, Q. Zhang, N. Odum, A.H. Rook, M.A. Wasik, Differential effects of interleukin-2 and interleukin-15 versus interleukin-21 on CD4+ cutaneous T-cell lymphoma cells, Cancer Res. 68 (4) (2008) 1083–1091.
[255] M. Baggiolini, I. Clark-Lewis, Interleukin-8, a chemotactic and inflammatory cytokine, FEBS Lett. 307 (1) (1992) 97–101.
[256] K. Wolk, H. Mitsui, K. Witte, S. Gellrich, N. Gulati, D. Humme, E. Witte, M. Gonsior, M. Beyer, M.E. Kadin, H.D. Volk, J.G. Krueger, W. Sterry, R. Sabat, Deficient cutaneous antibacterial competence in cutaneous T-cell lymphomas: role of Th2-mediated biased Th17 function, Clin. Cancer Res. 20 (21) (2014) 5507–5516.
[257] M.H. Fanok, A. Sun, L.K. Fogli, V. Narendran, M. Eckstein, K. Kannan, I. Dolgalev, C. Lazaris, A. Heguy, M.E. Laird, M.S. Sundrud, C. Liu, J. Kutok, R.S. Lacruz, J. A. Latkowski, I. Aifantis, N. Odum, K.B. Hymes, S. Goel, S.B. Koralov, Role of dysregulated cytokine signaling and bacterial triggers in the pathogenesis of cutaneous T-Cell lymphoma, J. Invest. Dermatol. 138 (5) (2018) 1116–1125.
[258] M.L. Castellani, P. Felaco, R.J. Galzio, D. Tripodi, E. Toniato, M.A. De Lutiis, M. Fulcheri, A. Caraffa, P. Antinolfi, S. Tete, M. Felaco, F. Conti, F. Pandolfi, T. C. Theoharides, Y.B. Shaik-Dasthagirisaheb, IL-31 a Th2 cytokine involved in immunity and inflammation, Int. J. Immunopathol. Pharmacol. 23 (3) (2010) 709–713.
[259] J. Richmond, et al., Interleukin-16 as a marker of Sézary Syndrome onset and stage, J Clin Immunol (2011), https://doi.org/10.1007/s10875-010-9464-8.