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Lessons learned from gene expression profiling of cutaneous T-cell lymphoma

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Abstract

Gene expression studies of cutaneous T-cell lymphoma (CTCL) span a decade, yet pathogenesis is poorly understood and diagnosis remains a challenge. This review examines the varied approaches to gene expression analysis of CTCL, with emphasis on cell populations, control selection, and expression data collection. Despite discordant results, several dysregulated genes have been identified across multiple studies including *PLS3*, *KIR3DL2*, *TWIST1*, and *STAT4*. Here, we provide an overview of the most consistently expressed genes across different studies and bring them together through common pathways biologically relevant to CTCL. Four pathways, evasion of activation-induced cell death, T-helper 2 lymphocyte differentiation, TGF- β receptor expression, and TNF receptor ligands, appear to encompass the most frequently affected genes, hypothetically providing insight to the disease pathogenesis.

Keywords

Cutaneous T-cell lymphoma; gene expression; transcriptome; Sézary syndrome; mycosis fungoides

Introduction

Characterization of the pathophysiology and genetic abnormalities of rare malignancies is often slow as disease complexity is difficult to surmount with a small number of studies. Cutaneous T-cell lymphoma represents a group of diseases in which a number of gene expression studies have been conducted but pathogenesis is still poorly understood.

Mycosis fungoides (MF) and Sézary syndrome (SS) are the two most common clinical variants of cutaneous T-cell lymphoma (CTCL), a rare group of lymphomas with 2,000 new cases in the United States each year.¹² MF generally has an indolent disease course in early stages, but rapid progression and extracutaneous dissemination of malignant T-cells can occur.¹³ SS is a leukemic and erythrodermic variant of CTCL, characterized by the presence of a clonal population of Sézary cells, circulating malignant lymphocytes. SS is aggressive with a survival time of 2–4 years following diagnosis.¹³ Despite advances in chemotherapeutic and biologic approaches to SS treatment, care remains palliative and not curative. Early detection is associated with positive clinical outcome,¹⁴ but diagnosis is complicated by histological and clinical similarities with other dermatoses.¹⁵ The identification of biomarkers that could aid in early detection of MF and SS may significantly improve diagnostic accuracy and clinical outcomes. Further, the relationship between SS

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Conflict of Interest

The authors disclose no conflict of interest.

and MF remains controversial. Though each has a distinctive clinical presentation, SS is often designated as the leukemic form of MF. Recent studies have produced differing and sometimes conflicting opinions. While some investigators demonstrate that the two are genetically diverse,^{16,17} overlaps have also been identified in the areas of gene expression, protein translation, and non-coding RNA expression.⁶

The etiology of CTCL remains unknown. Viruses have been implicated in etiology of CTCL; however, using digital transcriptome subtraction and next generation sequencing technologies, our group and others have not found genome-integrated viruses with a potential oncogenic role involved in pathogenesis of CTCL.^{6,18} However, these studies do not exclude a possibility of other chronic antigen-driven causality, including non-integrated viruses.

Numerous genetics studies over the last ten years have attempted to characterize gene expression in CTCL. The aims of these studies have been four-fold: (1) to establish biomarkers that may be useful in the diagnosis of SS and MF, (2) to reveal genes important to disease pathogenesis, (3) to examine genetic relationships between these two entities, and (4) to discover potential targets for therapy. These genetic studies have yielded discordant results. One of the barriers to effective analysis of genetic data is the lack of standard approaches to both the selection of patient population and evaluation of patients' samples. Improved consistency of approaches would enable comparison between different studies and data consolidation possibly unveiling important facts obscured by the heterogeneity of current methods. At this time, to advance further and to propose future directions in genetic studies in CTCL, it is necessary to scrutinize the data produced in various studies and to analyze how it fits within the current state of the field.

This review summarizes gene expression studies conducted in MF and SS up to date, examines potential reasons for the discordant results, offering potential solutions to this problem, and organizes the data through integrated biologically relevant pathway analysis. Understanding of commonly found abnormal gene expressions may be relevant to disease pathogenesis and provide a springboard for the future genetic studies in CTCL.

Gene expression studies in MF and SS

CTCL gene expression studies conducted thus far have used a variety of methods; there has been little uniformity in the field with regard to cell population selection, control selection, and transcriptome analysis approaches. These discrepancies likely contribute considerably to the disagreement in results.

The selection of cell population has varied widely among CTCL gene expression studies. Studies have utilized peripheral blood mononuclear cells (PBMCs) from SS and MF patients,^{19–21} SS and MF skin samples,^{10,16,21–24} or a subpopulation of T-cells, such as CD4+ cells.^{17,21,23,25,26} Gene expression in SS and MF cell lines has also been characterized.^{25,27}

In addition to variance in cell populations, studies have also selected different controls. Often studies compare CTCL cells with their counterparts in normal samples. For example, SS CD4+ cells have been compared to CD4+ cells from healthy controls,^{17,21,25} and CTCL skin samples to normal skin.^{23,24} SS PBMCs have also been compared with Th2-skewed PBMCs from normal controls, as characteristics of advanced SS are associated with a Th2-polarized immune response.¹⁹ In addition, phytohemagglutinin, a known T-cell activator,²⁸ has been applied to healthy control peripheral T cells prior to gene expression analysis.¹⁷ Other studies have compared CTCL samples with samples from patients with inflammatory skin diseases such as psoriasis, atopic dermatitis, and erysipelas.^{10,17,21,23,24} To distinguish

the various stages of CTCL from one another, MF and SS patient samples have also been compared directly.²²

Gene expression studies in CTCL has proved not only heterogeneity between patients but also significant diversity of gene expression within the same patient. For example, expression of *PLS3*, the most consistently reported upregulated gene in SS patients, was identified in only 60% of SS patients and 38% of MF patients with peripheral blood involvement using CD4+ T-cells in a recent study by Jones *et al.* Further, heterogeneity of expression of *PLS3* was observed within the same malignant population isolated from the same patient.⁹ As there is no single suitable marker for isolation of a pure population of CTCL tumor cells, different studies have utilized different approaches. Each approach has its merits for answering certain questions, but not others. For example, the comparison of SS PBMCs to normal PBMCs as performed by Nebozhyn *et al.* successfully yielded information about which genes represent biomarkers that may aid in disease diagnosis or prognosis.²⁹ In their study, Nebozhyn *et al.* performed comparison of SS PBMCs to normal PBMCs and identified a group of five genes that can reliably diagnose CTCL using quantitative PCR. Importantly, genetic variation observed in bulk PBMCs may or may not be attributable specifically to the malignant CD4+ T-cells, as they also contain non-malignant cells, macrophages and monocytes, but rather to the advanced age or inflammatory state of patient population.³⁰

To minimize heterogeneity and identify pathogenic gene dysregulation, some studies have isolated subpopulations of T-cells from the patients with SS and normal controls. This approach was applied by Wang *et al.* who compared gene expression in SS CD4+CD7- cells to normal CD4+ cells to identify downregulation of *SATB1*, a regulator of T-cell development and maturation that produces apoptosis resistance in SS. Similarly to using bulk PBMCs, the CD4+ cells in SS patients are themselves heterogeneous and do not consist exclusively of malignant Sézary cells; therefore, gene dysregulation of the malignant population may be obscured by the inclusion of nonmalignant cells. More recently, a new approach was employed by Pomerantz *et al.* in which subpopulations of malignant and nonmalignant CD4+ cells from a SS patient were compared with one another.³¹ Specifically, Pomerantz *et al.* isolated CD4+CD45RO+ TCRV β -defined malignant cells from a patient's own CD4+CD45RO+ nonmalignant cells; the nonmalignant cells then serve as an internal control, effectively eliminating the heterogeneity that is seen when an SS patient is compared to a normal control. While the CD4+CD7- and TCRV β -based approaches do yield representative populations that are more specific than bulk PBMC analysis, these markers may be expressed by some non-malignant cells and are not uniformly expressed by the entire malignant population. Additionally, though the methods that center on a subpopulation of T-cells are best suited for studying disease pathogenesis, they may not be fitting for biomarker analysis.

When skin samples are utilized in gene expression analysis of CTCL, determination of which genes are specific to the malignant T-cell infiltrate can be even more difficult. In early patch/plaque lesions, this infiltrate can account for less than 10% of the skin sample,¹⁰ and while this percentage is significantly higher in tumors, a skin sample is usually contaminated by non-malignant cells such as keratinocytes, melanocytes and Langerhans cells. To eliminate the signal from keratinocytes and other normal surrounding tissue, normalization should be performed.^{10,11}

Using SS cell lines for genetic analysis is also a challenge. It has been demonstrated that while there are shared transcriptomic features among SS cell lines and patient samples, not all SS cell gene expression alterations are preserved in cell lines.²⁵ In fact, the Sézary cell line Hut78 lacks increased expression of *PLS3*.²⁵

Analysis of Differentially Expressed Genes

Despite the differences in CTCL transcriptome studies, a number of genes have been consistently reported across multiple studies. Table 1 shows a selection of gene expression changes found in at least two transcriptomic studies of SS and MF patients as well as CTCL cell lines in order of their level of expression and frequency. A number of these genes, many of which are known oncogenes, have been studied functionally in CTCL or tested as diagnostic biomarkers.²⁹ Several of these gene expression changes are seen in both MF and SS (*TWIST1*, *CD52*, *PTPRCAP*, *JUNB*, *TOX*), while others are limited to either MF or SS, and still others show differential expression between MF and SS (*EPHA4*, *STAT4*). Several studies reported opposite results for the same genes. For example, *NEDD4L* and *KIR3DL2* have been found both upregulated and downregulated in SS.^{6,17,20,21}

To reconcile the results of these studies, we used Ingenuity Pathway Analysis (IPA) to identify pathways that may be important in CTCL pathogenesis and may be considered for future study based on all of the differentially expressed genes in twelve gene expression studies.^{6,16,17,19–22,25–27,29,31} All included genes were identified with microarray-based transcriptome analysis and/or qRT-PCR and had expression levels 2 times greater or less than normal controls. A selection of canonical pathways that were significantly affected (all had $p\text{-value} < 0.0005$) and the genes involved are displayed in table 2.

IPA was also applied to determine the relationship between identified genes (Fig. 1). Interestingly, direct and indirect relationships were identified amongst our inclusive list of differentially expressed genes. Fig. 2 provides a simplified overview of several key players in CTCL.

The following pathways were specifically highlighted as a result of our analysis:

- Evading activation-induced cell death.** *SATB1* expression is consistently decreased in SS, and this decreased expression is shown to have downstream effects on *FasL*.²⁵ *FasL* and its receptor *Fas/CD95*, which is also downregulated in CTCL,^{32,33} play a role in T-cell homeostasis via T-cell receptor (TCR) related activation-induced cell death (AICD).³⁴ TCR stimulation normally increases *FasL* expression, but this response is absent in CTCL.³⁵ Moreover, *FasL* expression is negatively regulated by *JUNB*, which is upregulated in CTCL (Fig. 2).³⁶ Decreased or delayed *FasL* expression on the surface of SS cells affords protection from AICD.³⁵ Further, when *FasL* is expressed by SS or MF cells, a correlated loss of CD8+ T-cells via bystander cytotoxicity is observed, suggesting a second role of *FasL* in disease pathogenesis and progression.³⁷ NF- κ B, a transcription factor that protects against apoptosis via AICD, is constitutively active in CTCL cell lines and SS PBMCs³⁸ which provides further evidence that evasion of this pathway is important in CTCL pathogenesis. *BCL2* has also been implicated blocking AICD, but contrasting findings on *BCL2* expression as both upregulated and downregulated indicate that *BCL2* loss can be compensated by other antiapoptotic mechanisms.
- T-helper 2 lymphocyte differentiation and immune activation.** The activity of increased *JUNB* expression in CTCL extends beyond *FasL* regulation. *JUNB* also promotes T-cell differentiation, particularly T-helper 2 lymphocyte differentiation,³⁹ a key feature of the malignant cells in CTCL.⁴⁰ Th2-skewing is further enhanced by a decrease in *STAT4* which acts as a transcription factor required for Th1 differentiation (Fig. 2).^{41,42} *JUNB* also regulates *NFAT*, a nuclear factor which mediates cellular activation and the immune response.⁴³ Treatment of CTCL cell lines and patient samples with *NFAT* siRNA has resulted in decreased

T-plastin (*PLS3*) expression, an important observation as *PLS3* remains the most consistently reported upregulated gene in all expression studies. Following NFAT siRNA-produced T-plastin decrease, subsequent increased susceptibility to apoptosis and decreased cell motility occur.⁴⁴ Many of the genes noted to increase in CTCL, including *PLS3*, *DNM3*, *VCAN*, and *EPHA4*, are implicated in cell motility and may contribute to the ability of malignant CD4+ T-cells to home to the skin.^{45–49} Studies similar to the one on *PLS3* have not yet been conducted with other genes that may contribute to cell migration, motility, or invasion and represent an area of potential future study.

- **TGF- β receptor expression.** In lymphoid cells, TGF- β acts as an antiproliferative and proapoptotic cytokine⁵⁰ by blocking IL-2 production and the maturation of T-cells.⁵¹ These functions are lost in CTCL cells that fail to express the TGF- β receptor II protein (*TGFB2*).^{26,52} Sequencing of the *TGFB2* mRNA expressed in cells isolated from the skin nodule of a patient with MF showed an inhibitory mutation that blocked the normal function of the receptor (Fig. 2).⁵³ Further, the loss of expression of two of *TGFB2*'s downstream targets, *SMAD3* and *SMAD7*,²⁶ is suggestive of an important role of this pathway in CTCL pathogenesis.
- **TNF receptor ligands.** Increased expression of several TNF receptor ligands, particularly *TNFSF7/CD70*, *TNFSF11/RANKL*, and *TNFSF5/CD40L*, has been identified in CTCL. In SS T-cells, high levels of CD70 expression are coupled with increased expression of its receptor CD27.²⁶ CD70 interaction with CD27 results in T-cell proliferation and effector T-cell functions (Fig. 2).^{54,55} The state of immune activation that is produced by high levels of CD70 is exacerbated by concurrently high *RANKL* expression which enhances the costimulatory actions of dendritic cells.⁵⁶ CD40L has likewise been implicated in CTCL cell growth, as CD40/CD40L surface antigens have been observed on MF infiltrative lymphocytes allowing for stimulation between adjacent cells.⁵⁷ Further, CD40L may increase the skin-homing abilities of malignant T-cells as they move towards CD40-expressing skin resident Langerhans cells.⁵⁷

Differentially expressed pathways are interconnected

Our pathway analysis of differentially expressed genes in CTCL revealed complex interactions of many genes implicated in CTCL pathogenesis (Fig. 1) and demonstrated that they are intimately interconnected (Fig. 1 and 2). These pathways also indicate the potential contributions of gene expression alteration to CTCL pathogenesis.

Defects in apoptotic pathways are well-known and frequently observed abnormalities in numerous malignancies, including CTCL. Specifically, overexpression of oncogenes such as *JUNB* observed in several genomic studies in CTCL may be significant contributing factors to etiology of both MF and SS. Survival of malignant cells can be further augmented by escape from TGF- β regulation due to loss of *TGFB2*, TGF- β receptor II and its downstream targets, as well as defective TNF- α signaling pathways. Further escalation in proliferative capacity results from increased expression of TNF ligands may contribute to the malignant behavior of CTCL cells.

Innate immune responses on the skin may be triggered by “danger signals” such as viral or bacterial infection, resulting in creation of a proinflammatory environment, eventual recruitment of professional antigen presenting cells, such as dendritic cells, and initiation of adaptive immune responses.⁵⁸ Chronic antigenic stimulation results in constitutive

recruitment of memory T cells and, eventually, may lead to natural selection of a clone with survival advantages.⁵⁹

There are numerous abnormalities in gene expression profiling in support of the role of unknown chronic antigen, including the loss of expression of *SATB1* and *BCL2* their downstream targets that promote AICD, such as *FasL*. Together with overexpression of *JUNB*, they promote AICD escape. Importantly, some of the differentially expressed genes may be reflective of overall inflammatory state of CTCL (e.g. TNF pathway, CD40, IL1, and others), while others may be directly involved in the disease pathogenesis. For example, the Th2-skewed, immune activated phenotype seen in CTCL may be directly related to these changes in gene expression or may be secondary to chronic antigenic stimulation and overall proinflammatory environment observed in these diseases. It remains unclear whether genes related to inflammatory state are pathogenic or represent a downstream effect. Further studies to delineate the cause vs. effect relationships in CTCL are necessary to answer these questions.

Non-coding RNAs are also dysregulated in CTCL

In addition to studies on gene expression in CTCL, a number of studies have characterized the expression of noncoding RNAs in SS and MF, and differential expression of both microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) has been identified. Table 2 summarizes these studies. Identified noncoding RNAs have putative roles in CTCL pathogenesis and diagnosis. MiR-21, a miRNA which is upregulated in a large number of cancers, is upregulated in SS where its promoter is bound by STAT3.² Further, Narducci *et al.* found upregulation of miR-21 to be a negative prognostic factor which was overexpressed in all patients with poor disease outcome and only one of seven with better outcome.³ Ballabio *et al.* reported that miR-342, miR-17-5p are downregulated in SS, and correction of this downregulation produces apoptosis,¹ while Manfe *et al.* implicated miR-122 in protection from chemotherapy-induced apoptosis in CTCL cells.⁷ MiR-155 upregulation was identified by van Kester *et al.*,⁵ and a recent study by Kopp *et al.* demonstrated that aberrant activation of STAT5 in tumor cells drives this increased mir-155 expression, promoting tumor cell proliferation.⁸ These results indicate that therapeutic strategies aimed at miRNAs or their downstream effectors may increase efficacy of current chemotherapeutic approaches. A number of miRNAs have been shown to distinguish CTCL from healthy controls or benign dermatoses. Importantly, a five-miRNA panel (miR-326, miR-663b, miR-711, miR-203, miR-205) reported by Ralfkiaer *et al.* was largely unaffected by drug treatment, indicating diagnostic potential that would spare patients from a drug-free period before a diagnostic biopsy.⁴ While the number of studies examining noncoding RNAs expression in CTCL is still relatively small, the results produced so far indicate that miRNAs and lncRNAs are important in CTCL pathogenesis and should be explored further.

Future Studies

Although gene expression studies thus far have yielded differing results, there are some consensus gene changes that have been observed repeatedly both in MF and SS. This review highlights and brings together those gene expression changes and outlines the reasons for variations in the results in studies to-date. As we look to the future of gene expression studies in CTCL, tailoring of population selection, controls, and methodology to a specific goal will provide a basic framework for the structuring of future gene expression studies.

To establish biomarkers that may be diagnostically useful, crude samples, such as whole PBMCs or whole skin in CTCL are appropriate to study in comparison with normal healthy controls and with similar pathological processes, such as with dermatoses that clinically

resemble CTCL. Special consideration should be given to those biomarkers that are easy to measure, such as cell surface markers that can be analyzed using flow cytometry or proteins easily visualized with immunohistochemistry. To reveal genes important to disease pathogenesis, it is best to evaluate purified malignant cells in close comparison with non-malignant cells. Such genetic analysis of purified malignant population may enable evaluation of genetic relationships between subtypes of malignancy and to discover potential targets for therapy. In CTCL, an appropriate subpopulation lies within CD4⁺ T-cells most of the time; more specifically, within clonal TCR- $\nu\beta$ -restricted malignant cells. However, such purification is not always possible due to technical limitations (e.g. antibodies for TCR- $\nu\beta$ are not available for all rearrangements.) Control groups for these experiments may be CD4⁺ cells from healthy controls or, when TCR- $\nu\beta$ typing is used, a patient's own non-malignant cells. Again, this approach is not without limitations. While using a patient's non-malignant cells as control eliminate person-person gene expression heterogeneity, the cells are likely to be affected by the tumor microenvironment and may not represent normal T-cells. Therefore, ongoing integration of data sets generated with both study approaches, such as those used to compile this review, is warranted.

Though MF and SS are rare malignancies in which gene expression studies have been difficult, studies to date have identified important genes and pathways relevant to etiology and pathogenesis of these diseases. We are optimistic that in the nearest future, detailed functional studies delineating particular roles of the involved genes in CTCL will shed light on the questions at hand and will provide not only clues to the diagnosis and prognosis to CTCL, but also yield targets for effective therapies for CTCL as well as hope for its cure.

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References

1. Ballabio E, Mitchell T, van Kester MS, et al. MicroRNA expression in Sezary syndrome: identification, function, and diagnostic potential. *Blood*. 2010; 116:1105–13. [PubMed: 20448109]
2. van der Fits L, van Kester MS, Qin Y, et al. MicroRNA-21 expression in CD4⁺ T cells is regulated by STAT3 and is pathologically involved in Sezary syndrome. *J Invest Dermatol*. 2011; 131:762–8. [PubMed: 21085192]
3. Narducci MG, Arcelli D, Picchio MC, et al. MicroRNA profiling reveals that miR-21, miR486 and miR-214 are upregulated and involved in cell survival in Sezary syndrome. *Cell death & disease*. 2011; 2:e151. [PubMed: 21525938]
4. Ralfkiaer U, Hagedorn PH, Bangsgaard N, et al. Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL). *Blood*. 2011; 118:5891–900. [PubMed: 21865341]
5. van Kester MS, Ballabio E, Benner MF, et al. miRNA expression profiling of mycosis fungoides. *Molecular oncology*. 2011; 5:273–80. [PubMed: 21406335]
6. Lee CS, Ungewickell A, Bhaduri A, et al. Transcriptome sequencing in Sezary syndrome identifies Sezary cell and mycosis fungoides-associated lncRNAs and novel transcripts. *Blood*. 2012; 120:3288–97. [PubMed: 22936659]
7. Manfe V, Biskup E, Rosbjerg A, et al. miR-122 regulates p53/Akt signalling and the chemotherapy-induced apoptosis in cutaneous T-cell lymphoma. *PloS one*. 2012; 7:e29541. [PubMed: 22235305]
8. Kopp KL, Ralfkiaer U, Gjerdrum LM, et al. STAT5-mediated expression of oncogenic miR-155 in cutaneous T-cell lymphoma. *Cell cycle (Georgetown, Tex)*. 2013; 12:1939–47.
9. Jones CL, Ferreira S, McKenzie RC, et al. Regulation of T-plastin expression by promoter hypomethylation in primary cutaneous T-cell lymphoma. *J Invest Dermatol*. 2012; 132:2042–9. [PubMed: 22495182]

10. Tracey L, Villeundas R, Dotor AM, et al. Mycosis fungoides shows concurrent deregulation of multiple genes involved in the TNF signaling pathway: an expression profile study. *Blood*. 2003; 102:1042–50. [PubMed: 12689942]
11. van Kester MS, Borg MK, Zoutman WH, et al. A Meta-Analysis of Gene Expression Data Identifies a Molecular Signature Characteristic for Tumor-Stage Mycosis Fungoides. *J Invest Dermatol*. 2012; 132:2050–9. [PubMed: 22513784]
12. Willemze R, Jaffe ES, Burg G, et al. WHO-ERTC classification for cutaneous lymphomas. *Blood*. 2005; 105:3768–88. [PubMed: 15692063]
13. Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sézary syndrome: clinical prognostic factors and risk for disease progression. 2003; 139:857–66.
14. Foss FM. An oncologist's approach to therapy for cutaneous T-cell lymphoma. *Clin Lymphoma*. 2000; (Suppl 1):S9–14. [PubMed: 11707857]
15. Foss FM, Sausville EA. Prognosis and staging of cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am*. 1995; 9:1011–9. [PubMed: 8522481]
16. van Doorn R, van Kester MS, Dijkman R, et al. Oncogenomic analysis of mycosis fungoides reveals major differences with Sezary syndrome. *Blood*. 2009; 113:127–36. [PubMed: 18832135]
17. Booken N, Gratchev A, Utikal J, et al. Sezary syndrome is a unique cutaneous T-cell lymphoma as identified by an expanded gene signature including diagnostic marker molecules CDO1 and DNM3. *Leukemia*. 2008; 22:393–9. [PubMed: 18033314]
18. Mirvish ED, Pomerantz RG, Geskin LJ. Lack of novel merkel cell polyomavirus in mycosis fungoides tumors. *J Invest Dermatol*. 2010; 130:S29.
19. Kari L, Loboda A, Nebozhyn M, et al. Classification and Prediction of Survival in Patients with the Leukemic Phase of Cutaneous T Cell Lymphoma. *J Exp Med*. 2003; 197:1477–88. [PubMed: 12782714]
20. Mao X, Orchard G, Mitchell TJ, et al. A genomic and expression study of AP-1 in primary cutaneous T-cell lymphoma: evidence for dysregulated expression of JUNB and JUND in MF and SS. *J Cutan Pathol*. 2008; 35:899–910. [PubMed: 18494816]
21. Hahtola S, Tuomela S, Elo L, et al. Th1 Response and Cytotoxicity Genes are Down-Regulated in Cutaneous T-Cell Lymphoma. *Clin Cancer Res*. 2006; 12:4812–21. [PubMed: 16914566]
22. Shin J, Monti S, Aires DJ. Lesional gene expression profiling in cutaneous T-cell lymphoma reveals natural clusters associated with disease outcome. *Blood*. 2007; 110:3015–27. [PubMed: 17638852]
23. Goswami M, Duvic M, Dougherty A, et al. Increased Twist expression in advanced stage of mycosis fungoides and Sezary syndrome. *J Cutan Pathol*. 2012; 39:500–7. [PubMed: 22515221]
24. Zhang Y, Wang Y, Yu R, et al. Molecular Markers of Early-Stage Mycosis Fungoides. *J Invest Dermatol*. 2012; 132:1698–706. [PubMed: 22377759]
25. Wang Y, Su M, Zhou LL, et al. Deficiency of SATB1 expression in Sezary cells causes apoptosis resistance by regulating FasL/CD95L. *Blood*. 2010; 117:3826–35. [PubMed: 21270445]
26. van Doorn R, Dijkman R, Vermerr MH, et al. Aberrant Expression of the Tyrosine Kinase Receptor EphA4 and the Transcription Factor Twist in Sezary Syndrome Identified by Gene Expression Analysis. *Cancer Res*. 2004; 64:5578–86. [PubMed: 15313894]
27. Mao X, Orchard G, Lillington DM, et al. BCL and JUNB abnormalities in primary cutaneous lymphomas. *British Journal of Dermatology*. 2004; 151:546–56. [PubMed: 15377339]
28. Gery I, Gershon RK, Waksman BH. Potentiation of the T-lymphocyte Response to Mitogens. *J Exp Med*. 1972; 136:128–42. [PubMed: 5033417]
29. Nebozhyn M, Loboda A, Kari L, et al. Quatitative PCR on 5 genes reliably identifies CTCL patients with 5% to 99% circulating tumor cells with 90% accuracy. *Blood*. 2006; 107:3189–96. [PubMed: 16403914]
30. Geskin LJ, Akilov OE, Linzer DE, et al. Age-matched multiplex analysis reveals global immune dysregulation in patients with CTCL. *SID*. 2011; 131:S92.
31. Pomerantz RG, Mirvish ED, Erdos G, et al. Novel approach to gene expression profiling in Sezary syndrome. *British Journal of Dermatology*. 2010; 163:1090–4. [PubMed: 20698843]

32. Wu J, Nihal M, Siddiqui J, et al. Low FAS/CD95 expression by CTCL correlates with reduced sensitivity to apoptosis that can be restored by FAS upregulation. *J Invest Dermatol.* 2009; 129:1165–73. [PubMed: 18923451]
33. Zoi-Toli O, Vermeer MH, De Vries E, et al. Expression of Fas and Fas-ligand in primary cutaneous T-cell lymphoma (CTCL): association between lack of Fas expression and aggressive types of CTCL. *The British journal of dermatology.* 2000; 143:313–9. [PubMed: 10951138]
34. El-Khatib M, Stanger BZ, Dogan H, et al. The molecular mechanism of FasL-mediated cytotoxicity by CD4+ Th1 clones. *Cell Immunol.* 1995; 163:237–44. [PubMed: 7541726]
35. Klemke C-D, Brenner D, Weib E-M, et al. Lack of T-cell Receptor-Induced Signaling is Crucial for CD95 Ligand Up-regulation and Protects Cutaneous Lymphoma Cells from Activation-Induced Cell Death. *Cancer Res.* 2009; 69:4175–83. [PubMed: 19435902]
36. Lotem J, Sachs L. Different mechanisms for suppression of apoptosis by cytokines and calcium mobilizing compounds. *Proc Natl Acad Sci USA.* 1998; 95:4601–6. [PubMed: 9539784]
37. Ni X, Hazarika P, Zhang C, et al. Fas ligand expression by neoplastic T lymphocytes mediates elimination of CD8+ cytotoxic T lymphocytes in mycosis fungoides: A potential mechanism of tumor immune escape? *Clin Cancer Res.* 2001; 7:2682–92. [PubMed: 11555580]
38. Sors A, Jean-Louis F, Pellet C, et al. Down-regulating constitutive activation of the NF-kappaB canonical pathway overcomes the resistance of cutaneous T-cell lymphoma to apoptosis. *Blood.* 2006; 107:2354–63. [PubMed: 16219794]
39. Hartenstein B, Teurich S, Hess J, et al. Th2 cell-specific cytokine expression and allergen-induced airway inflammation depend on JunB. *EMBO J.* 2002; 21:6321–9. [PubMed: 12456639]
40. Vowel BR, Lessin SR, Cassin M, et al. Th2 Cytokine mRNA Expression in Skin in Cutaneous T-Cell Lymphoma. *J Invest Dermatol.* 1994; 103:669–73. [PubMed: 7963654]
41. Murphy KM, Ouyang W, Szabo SJ, et al. T helper differentiation and proliferation that is independent of its role in the maintenance of IL-12R beta 2 chain expression and signaling. *J Immunol.* 1999; 169:4388–98.
42. Nishikomori R, Usui T, Wu CY, et al. Activated STAT4 has an essential role in Th1 differentiation and proliferation that is independent of its role in the maintenance of IL-12R beta 2 chain expression and signaling. *J Immunol.* 2002; 169:4388–98. [PubMed: 12370372]
43. Bueno OF, Brandt EB, Rothenberg ME, et al. Defective T cell development and function in calcineurin A beta-deficient mice. *Proc Natl Acad Sci USA.* 2002; 99:9398–403. [PubMed: 12091710]
44. Begue E, Jean-Louis F, Bagot M, et al. Inducible expression and pathophysiologic function of T-plastin in cutaneous T-cell lymphoma. *Blood.* 2012; 120:143–54. [PubMed: 22627769]
45. Hafner C, Schmitz G, Meyer S, et al. Differential gene expression of eph receptors and ephrins in benign human tissues and cancers. *Clin Chem.* 2004; 50:490–9. [PubMed: 14726470]
46. Hirose J, Kawashima H, Yoshie O, et al. Versican interacts with chemokines and modulates cellular responses. *J Biol Chem.* 2001; 276:5228–34. [PubMed: 11083865]
47. Holen HL, Nustand K, Aasheim HC. Activation of EphA receptors on CD4+CD45RO+ memory cells stimulates migration. *J Leukoc Biol.* 2010; 87:1059–68. [PubMed: 20160140]
48. Lin CS, Lau A, Huynh T, et al. Differential regulation of human T-plastin gene in leukocytes and non-leukocytes: identification of the promoter, enhancer, and CpG island. *DNA Cell Biol.* 1999; 18:27–37. [PubMed: 10025506]
49. Orth JD, McNiven MA. Dynamin at the actin–membrane interface. *Curr Opin Cell Biol.* 2003; 15:31–9. [PubMed: 12517701]
50. Totth A, Sebestyen A, Barna G, et al. TGF beta 1 induced caspase-dependent but death-receptor independent apoptosis in lymphoid cells. *Anticancer Res.* 2001; 21:1207–12. [PubMed: 11396165]
51. Gorelik L, Flavell RA. Transforming growth factor beta in T-cell biology. *Nat Rev Immunol.* 2002; 2:46–53. [PubMed: 11905837]
52. Capocasale RJ, Lamb RJ, Vonderheid EC, et al. Reduced surface expression of transforming growth factor beta receptor type II in mitogen-activated T cells from Sézary patients. *Proc Natl Acad Sci USA.* 1995; 92. [PubMed: 7816855]

53. Knaus PI, Lindemann D, DeCoteau JF. A dominant inhibitory mutant of the type II transforming growth factor beta receptor in the malignant progression of a cutaneous T-cell lymphoma. *Mol Cell Biol.* 1996; 16:3480–9. [PubMed: 8668164]
54. Lens SM, Baars PA, Hooibrink B, et al. Antigen-presenting cell-derived signals determine expression levels of CD70 on primed T-cells. *Immunology.* 1997; 90:38–45. [PubMed: 9038710]
55. Tesselaar K, Xiao Y, Arens R, et al. Expression of the murine CD27 ligand CD70 in vitro and in vivo. *J Immunol.* 2003; 170:33–40. [PubMed: 12496380]
56. Josien R, Li HL, Ingulli E, et al. TRANCE, a tumor necrosis factor family member, enhances the longevity and adjuvant properties of dendritic cells in vivo. *J Exp Med.* 2000; 191:495–502. [PubMed: 10662795]
57. Storz M, Zepter K, Kamarashev J, et al. Coexpression of CD40 and CD40 ligand in cutaneous T-cell lymphoma (mycosis fungoides). *Cancer Res.* 2001; 61:452–4. [PubMed: 11212229]
58. Kupper TS, Fuhlbrigge RC. Immune surveillance in the skin: mechanisms and clinical consequences. *Nature reviews Immunology.* 2004; 4:211–22.
59. Lowe DB, Storkus WJ. Chronic inflammation and immunologic-based constraints in malignant disease. *Immunotherapy.* 2011; 3:1265–74. [PubMed: 21995576]
60. O'Neill BL, Mirvish ED, Pomerantz RG, et al. TOX, PLS3, and KIR3DL2 genes are differentially expressed in Sézary Syndrome. *J Invest Dermatol.* 2012; 132:S25.
61. Su M, Dorocicz I, Dragowska WH, et al. Aberrant Expression of T-Plastin in Sezary Cells. *Cancer Res.* 2003; 63:7122–7. [PubMed: 14612505]
62. Giganti A, Plastino J, Bassan J, et al. Actin-filament cross-linking protein T-plastin increased Arp2/3-mediated actin-based movement. *J Cell Science.* 2005; 118:1255–65. [PubMed: 15741236]
63. Loebel DA, Tsoi B, Wong N. A conserved noncoding intronic transcript at the mouse Dnm3 locus. *Genomics.* 2005; 2005:782–9. [PubMed: 15885504]
64. Kuratomi G, Komuro A, Goto K, et al. Nedd4-2 (neural precursor cell expressed, developmentally down-regulated 4-2) negatively regulates TGF- β (transforming growth factor- β) signalling by inducing ubiquitin-mediated degradation of Smad2 and TGF- β type I receptor. *Biochem J.* 2005; 386:461–70. [PubMed: 15496141]
65. Gao C, Pang L, Ren C, et al. Decreased expression of Nedd4L correlates with poor prognosis in gastric cancer patient. *Med Oncol.* 2012; 29:1733–8. [PubMed: 21909941]
66. Poszepczynska-Guigne E, Schiavon V, D'Incan M, et al. CD158k/KIR3DL2 Is a New Phenotypic Marker of Sezary Cells: Relevance for the Diagnosis and Follow-Up of Sezary Syndrome. *J Invest Dermatol.* 2004; 122:820–3. [PubMed: 15086570]
67. Mingari MC, Moretta A, Moretta L. Regulation of KIR expression in human T cells: a safety mechanism that may impair protective T-cell responses. *Immunol Today.* 1998; 19:153–7. [PubMed: 9577090]
68. Ni X, Richmond HM, Liao XM, et al. Induction of T-cell response against cutaneous T-cell lymphomas ex vivo by autologous dendritic cells transfected with amplified tumor mRNA. *J Invest Dermatol.* 2008; 128:2631–9. [PubMed: 18480841]
69. Vermeer MH, van Doorn R, Dijkman R, et al. Novel and highly recurrent chromosomal alterations in Sezary syndrome. *Cancer Res.* 2009; 69:2689–98. [PubMed: 18413736]
70. Maestro R, Dei Tos AP, Hamamori Y, et al. Twist is a potential oncogene that inhibits apoptosis. *Gene Dev.* 1999; 13:2207–17. [PubMed: 10485844]
71. Watanabe O, Imamura H, Shimizu T, et al. Expression of twist and wnt in human breast cancer. *Anticancer Res.* 2004; 24:3851–6. [PubMed: 15736421]
72. Jiang L, Yuan CM, Hubacheck J, et al. Variable CD52 expression in mature T cell and Nk cell malignancies: implication for alemtuzumab therapy. *Br J Haematol.* 2009; 2009:173–9. [PubMed: 19236377]
73. Kitamura K, Maiti A, Ng DH, et al. Characterization of the interaction between DC45 and CD45-AP. *J Biol Chem.* 1999; 274:21151–7. [PubMed: 7673147]
74. Motoya S, Kitamura KMA, et al. Interaction between DC45-AP and protein-tyrosine kinases involved in T cell receptor signaling. *J Biol Chem.* 1999; 274:14392–9. [PubMed: 10318863]

75. Summy JM, Gallick GE. Src family kinases in tumor pregression and metastasis. *Cancer Metastasis Rev.* 2003; 22:337–58. [PubMed: 12884910]
76. Voice J, Donnelly S, Dorsam G. c-Maf and JunB mediation of Th2 differentiation induced by the type 2 G protein-coupled receptor (VPAC2) for vasoactive intestinal peptide. *J Immunol.* 2004; 172:7289–96. [PubMed: 15187104]
77. Tesselaar K, Arens R, van Schijndel GM, et al. Lethal T cell immunodeficiency induced by chronic costimulation via CD27–CD70 interactions. *Nat Immunol.* 2003; 4:49–54. [PubMed: 12469117]
78. Chen A, Xu H, Choi Y, et al. TRANCE counteracts FasL-mediated apoptosis of murine bone marrow-derived dendritic cells. *Cell Immunol.* 2004; 231:40–8. [PubMed: 15919368]
79. Aliahmad P, Kaye J. Development of all CD4 T lineages requires nuclear factor TOX. *J Exp Med.* 2008; 205:245–56. [PubMed: 18195075]
80. Kim S, Takahashi H, Lin W, et al. Carcinoma-produced factors activate myeloid cells through TLR2 to stimulate metastasis. *Nature.* 2009; 457:102–6. [PubMed: 19122641]
81. Liu P, Keller JR, Ortiz M. Bcl11a is essential for normal lymphoid development. *Nat Immunol.* 2003; 4:525–32. [PubMed: 12717432]
82. Alvarez JD, Yasui DH, Niida H, et al. The MAR-binding protein SATB1 orchestrates temporal and spatial expression of multiple genes during T-cell development. *Gene Dev.* 2000; 14:521–35. [PubMed: 10716941]
83. Jones D, Dang NH, Duvic M, et al. Absence of CD26 Expression Is a Useful Marker for Diagnosis of T-Cell Lymphoma in Peripheral Blood. *Am J Clin Pathol.* 2001; 115:885–92. [PubMed: 11392886]
84. Sokolowska-Wojdylo M, Wenzel J, Gaffal E, et al. Absence of CD26 expression on skin-homing CLA+ CD4+ T lymphocytes in peripheral blood is a highly sensitive marker for early diagnosis and therapeutic monitoring of patients with Sézary syndrome. *Clin Exp Dermatol.* 2005; 30:702–6. [PubMed: 16197392]
85. Osella-Abate S, Zaccagna A, Savoia P, et al. Expression of apoptosis markers on peripheral blood lymphocytes from patients with cutaneous T-cell lymphoma during extracorporeal photochemotherapy. *J Am Acad Dermatol.* 2001; 44:40–7. [PubMed: 11148475]
86. Cory S, Adams JM. The Bcl2 family: regulators of the cellular life-or-death switch. *Nat Rev Cancer.* 2002; 2:647–56. [PubMed: 12209154]
87. van Slooten HJ, van de Vijver MJ, van de Velde CH, et al. Loss of Bcl-2 in invasive breast cancer is associated with high rates of cell death, but also with increased proliferative activity. *Br J Cancer.* 1998; 77:789–96. [PubMed: 9514059]
88. Sommer VH, Clemmensen OJ, Nielsen O, et al. In vivo activation of STAT3 in cutaneous T-cell lymphoma. Evidence for an antiapoptotic function of STAT3. *Leukemia.* 2004; 18:1288–95. [PubMed: 15141228]
89. Eriksen KW, Kaltoft K, Mikkelsen G, et al. Constitutive STAT3-activation in Sezary syndrome: tyrphostin AG490 inhibits STAT3-activation, interleukin-2 receptor expression and growth of leukemic Sezary cells. *Leukemia.* 2001; 15:787–93. [PubMed: 11368440]
90. Krejsgaard T, Ralfkiaer U, Clasen-Linde E, et al. Malignant cutaneous T-cell lymphoma cells express IL-17 utilizing the Jak3/Stat3 signaling pathway. *J Invest Dermatol.* 2011; 131:1331–8. [PubMed: 21346774]

What's already known about this subject?

Gene expression in cutaneous T-cell lymphoma (CTCL) has been explored in a variety of diverse studies. Not surprisingly, considering heterogeneous designs, results have also been discordant.

What does this study add?

This review reconciles the differences in approaches to gene expression profiling and integrates them in a state-of-the-art report. We not only summarize the most consistently expressed genes across different studies, but also bring them together through common biologically relevant pathway analysis. This review allows us to hypothesize how these commonly found abnormalities may be relevant to disease pathogenesis and provide a springboard for the future genetic studies in CTCL.

Fig. 1. Known relationships between dysregulated genes

IPA was conducted to determine the relationships between dysregulated genes in CTCL. Five genes, *SATB1* (blue), *BCL2* (magenta), *JUNB* (green), *TGFB2* (red), and *STAT4* (yellow), and their connections are highlighted.

Fig. 2. Key players in CTCL pathogenesis

Aberrant up or downregulation of these players in CTCL results in evasion of AICD and decreased apoptosis, increased cell motility and proliferation, and increased Th2 differentiation and immune activation.

Table 1

Dysregulated genes in CTCL and their biological relevance.

Gene	Expression Change	Biological Relevance
<i>PLS3</i>	Overexpressed in SS PBMCS ^{17,19,29,44} and SS CD4+ T-cells ^{17,25,26,60,61}	Actin-building protein not normally expressed in T-cells, ⁴⁸ promoter is demethylated ^{9,48} known role in actin structure elongation, ⁶² associated with SS cell survival and migration ⁴⁴
<i>DNM3</i>	Overexpressed in SS PBMCS ¹⁷ and SS CD4+ T-cells ^{17,25}	Acts at the actin-membrane interface and is involved in lamellipodia formation and cell motility, ⁴⁹ expression regulated by <i>TWIST1</i> ⁶³
<i>NEDD4L</i>	Overexpressed in SS PBMCS, ¹⁷ SS CD4+ T-cells, ^{17,25} and the Hut78 cell line, ²⁵ decreased expression in malignant SS cells ⁶	E3 ubiquitin ligase, negatively regulates TGF- β superfamily signaling, ⁶⁴ associated with other cancers ⁶⁵
<i>KIR3DL2</i>	Overexpressed in SS PBMCS ²⁰ and SS CD4+ T-cells, ^{26,60} increased number of receptors on SS PBMCS by flow cytometry, ⁶⁶ and decreased expression in SS PBMCS ²¹	Member of the killer cell Ig-like receptors that inhibit natural killer-mediated lysis after interaction with HLA-A, may prevent elimination of tumor cells ⁶⁷
<i>TWIST1</i>	Overexpressed in SS PBMCS, ²⁰ SS CD4+ T-cells, ^{25,26} the Hut78 cell line, ²⁵ and advanced MF/SS lesions; ²³ increased copy number of Twist locus in SS patients ^{16,26,68,69}	Transcription factor that inhibits the c-myc-induced apoptotic response by modulating the ARF/MDM2/p53 pathway, ⁷⁰ overexpressed in many other cancers ⁷¹
<i>CD52</i>	Overexpressed in MF skin samples ²¹ and malignant SS cells, ³¹ present on the majority of SS/MF cells by flow cytometry ⁷²	Glycoprotein on the surface of B and T lymphocytes; represents a therapeutic target via anti-CD52 antibody, alemtuzumab ⁷²
<i>PTPRCAP (CD45-AP)</i>	Overexpressed in SS PBMCS, ²⁰ malignant SS cells, ³¹ and MF skin samples ¹¹	Enhances the phosphate activity of CD45 (PTPRC) ⁷³ which then dephosphorylates Src kinases, leading to T-cell receptor signaling ⁷⁴ and, in cancers, increased tumor progression ⁷⁵
<i>JUNB</i>	Overexpressed in SS CD4+ T-cells, ²⁶ strong nuclear expression of protein via IHC in SS/MF ²⁷	Transcription factor that binds to the IL-4 promoter, with c-MAF increases expression of Th2 cytokines and Th2 differentiation ⁷⁶
<i>TNFSF7 (CD70)</i>	Overexpressed in SS PBMCS ²⁰ and CD4+ T-cells ²⁶	CD27 ligand, interaction with CD27 results in T-cell proliferation and increased effector T-cell functions, ^{54,55} constitutive expression leads to depletion of naïve T-cells ⁷⁷
<i>TNFSF11 (RANKL)</i>	Overexpressed in SS PBMCS, ¹⁷ SS CD4+ T-cells, ^{17,26} and malignant SS cells ⁶	Induces inappropriate immune activation via a costimulatory pathway in dendritic cells (DCs), ⁵⁶ blocks FasL-mediated apoptosis and leads to increased survival of DCs ⁷⁸
<i>TOX</i>	Overexpressed in SS CD4+ T-cells ⁶⁰ and MF skin samples, ²⁴ protein identified on IHC in MF but no other dermatoses ²⁴	Transcription factor necessary for development of CD4+ lineages, but not normally expressed in mature CD4+ cells ⁷⁹
<i>VCAN</i>	Overexpressed in SS PBMCS ¹⁹ and SS CD4+ T-cells ²⁶	Cell surface protein which binds L-selectin and regulates chemokine function, ⁴⁶ activates TLR2:TLR6 to induce myeloid cell secretion of TNF α , thereby promoting cancer metastasis ⁸⁰
<i>EPHA4</i>	Overexpressed in SS CD4+ T-cells ²⁶ and malignant SS cells, ⁶ decreased expression in MF skin samples ¹¹	Transmembrane protein-tyrosine kinase that is involved in neural migration and angiogenesis, ⁴⁵ found on T-cells and induce migration when bound to ligand ephrin-A1 ⁴⁷
<i>BCL11A</i>	Decreased expression in SS CD4+ T-cells ^{13; 14} and Hut78 cell line ²⁵	Zinc-finger transcription factor that is required for normal T cell development, transplants of BCL11A-deficient cells in mice produced T-cell leukemia ⁸¹
<i>SATB1</i>	Decreased expression in SS CD4+ T-cells, ^{25,26} malignant SS cells, ⁶ and Hut78 cell line ²⁵	Required for thymocyte development and important in Th2 cell activation, ⁸² upregulation in vitro resulted in increased <i>FasL</i> expression and apoptosis ²⁵
<i>CD26</i>	Decreased expression SS PBMCS ¹⁹ and SS CD4+ T-cells ²⁶ , decreased number of receptors by flow cytometry ^{83,84}	Diagnostically useful marker for MF/SS via flow cytometric screening ^{83,84}

Gene	Expression Change	Biological Relevance
<i>STAT4</i>	Decreased expression in SS PBMCs, ^{19,20,29} SS CD4+ T-cells, ^{25,26} and malignant SS cells, ⁶ overexpressed in MF skin samples ¹⁰	Transcription factor required for Th1 differentiation ^{41,42}
<i>BCL2</i>	Decreased expression in SS PBMCs ¹⁹ , absent nuclear expression of protein via IHC in SS/MF, ²⁷ copy number loss in SS and PNO cell line ²⁷ high expression is a negative prognostic factor in patients on extracorporeal photopheresis ⁸⁵	Antiapoptotic, inner mitochondrial membrane protein that prevents apoptosis induced by cytotoxic agents; ⁸⁶ in breast cancer, loss of BCL2 expression correlates with increased apoptotic and necrotic cell death with a concurrent high proliferation rate ⁸⁷
<i>TGFBR2</i>	Decreased expression in SS CD4+ T cells ²⁶ and malignant SS cells, ⁶ decreased number of receptors by flow cytometry ⁵²	Known tumor suppressor with ligand (TGFβ1) and downstream signaling components (SMAD3 and SMAD7) that are also decreased, ²⁶ resulting in loss of growth inhibition ⁵⁰
<i>STAT3</i>	Activated in tumor stage MF ⁸⁸ and SeAx SS cell line ⁸⁹	Protects MF tumor cells from apoptosis in vitro, ⁸⁸ Inhibition of STAT3 reduces production of the pro-inflammatory cytokine IL-17 ⁹⁰

Table 2

Pathways implicated in CTCL based on transcriptome profiling

Pathway	Genes involved
T-Helper Cell Differentiation	<i>CD40, CD40LG, GATA3, STAT1, STAT4, TBX21, TGFB2</i>
Death Receptor Signaling	<i>BCL2, BIRC3, FAS, NAIP, TNFSF10</i>
p38 MAPK Signaling	<i>CREBBP, DUSP1, FAS, IL1R1, STAT1, TGFB2</i>
NF-KB Signaling	<i>CD40, CD40LG, CREBBP, IL1R1, LCK, TGFB2, TNFSF11</i>
Apoptosis Signaling	<i>BCL2, BIRC3, FAS, NAIP, MCL1</i>
IL-15 Signaling	<i>BCL2, IL2RB, LCK, STAT5B</i>

Table 3

Summary of studies on non-coding RNA in CTCL

	Experimental Design	Results
Ballabio ¹	MicroRNA microarray analysis of SS samples	miR-342 is negatively regulated in SS by miR-199a, correction of miR-342 and miR-17-5p downregulation results in apoptosis in SS
van der Fits ²	Chromatin immunoprecipitation of SeAx cells with STAT3 antibodies	STAT3 binds miR-21 in SS cells, miR-21 expression is increased in SS cells
Narducci ³	MicroRNA microarray analysis of SS samples	miR-21 expression is increased in SS cells and may be negative prognostic marker, miR-214 and miR-486 are upregulated in SS
Ralfkiaer ⁴	MicroRNA microarray analysis of SS samples	MiR-326, miR-663b, and miR-711 are induced in CTCL; miR-203 and miR-205 are repressed in CTCL; these five miRs can reliably distinguish CTCL and benign skin disease with 90% accuracy
van Kester ⁵	MicroRNA microarray analysis of MF samples	MiR-155, miR-92, and miR-93 are upregulated in MF
Lee ⁶	Transcriptome sequencing of SS samples	21 SC-associated annotated lncRNAs, and 12 undescribed putative lncRNAs identified in SS samples with >60% matching in MF samples
Manfe ⁷	CTCL cell line-based model of apoptosis and subsequent microarray	miR-122 is upregulated during induction of apoptosis in CTCL cell lines and decreases sensitivity to chemotherapy