Angiogenesis in cutaneous T-cell lymphoma - proteomic approaches (Review)

CRISTIANA TANASE[1,2], IONELA DANIELA POPESCU[1], ANA-MARIA ENCIU[1,3], ANCUTA AUGUSTINA GHEORGHISAN-GALATEANU[3,4], ELENA CODRICI[1], SIMONA MIHAI[1], LUCIAN ALBULESCU[1], LAURA NECULA[1,5] and RADU ALBULESCU[1,6]

[1]Department of Biochemistry-Proteomics, 'Victor Babes' National Institute of Pathology, 050096 Bucharest; [2]'Titu Maiorescu' University, Faculty of Medicine, 004051 Bucharest; [3]Department of Cellular and Molecular Medicine, 'Carol Davila' University of Medicine and Pharmacy, 050047 Bucharest; [4]'C.I. Parhon' National Institute of Endocrinology, 011863 Bucharest; [5]Department of Cellular and Molecular, 'Stefan S. Nicolau' Institute of Virology, 030304 Bucharest; [6]National Institute for Chemical-Pharmaceutical Research and Development, 061323 Bucharest, Romania

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Abstract. Neoangiogenesis plays an important role in cutaneous lymphoma pathogenesis. Cutaneous T-cell lymphoma (CTCL) is characterized by the presence of malignant T-cell clones in the skin. Vascular microenvironment of lymphomas accelerates neoangiogenesis through several factors released by tumoral cells: VEGF family, bFGF and PIGF. Tumor stroma (fibroblasts, inflammatory and immune cells) also plays a crucial role, by providing additional angiogenic factors. The angiogenic process through the VEGF-VEGFR axis can promote survival, proliferation and metastasis via autocrine mechanisms in cutaneous lymphomas. Microvascular density (MVD) measures the neo-vascularization of cutaneous lymphoma, generated by the response of tumor cells, proangiogenic stromal cells, and benign T/B lymphocytes within the tumor inflammatory infiltrate. Pro-angiogenic proteins have been found to indicate the evolution and prognosis in patients with CTCL. In conclusion, anti-angiogenic therapeutic protocols can target tumor vasculature or malignant tumor cells directly or through a large number of combinations with other drugs. The integration of proteomics into clinical practice based on high-throughput technologies leads to the development of personalized medicine, adapting the specific biomarkers to the application of cancer-type specific individual drug targets.

Correspondence to: Professor Cristiana Tanase, Department of Biochemistry-Proteomics, 'Victor Babes' National Institute of Pathology, 99-101 Splaiul Independentei, 050096 Bucharest, Romania
E-mail: bioch@vbabes.ro

Abbreviations: VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; bFGF, basic fibroblast growth factor; PIGF, placenta growth factor; STAT, signal transducer and activator of transcription; JAK, Janus kinase; CCL20, chemokine (C-C motif) ligand 20; CCR6, C-C motif chemokine receptor 6; PDPN, podoplanin; LYVE-1, lymphatic vessel hyaluronan receptor-1; LTα, lymphotoxin-α; CXCR4, C-X-C chemokine receptor type 4; CXCL12, C-X-C motif chemokine ligand 12; TP53, tumor protein p53; RB1, retinoblastoma protein 1; PTEN, phosphatase and tensin homolog; DNMT3A, DNA methyltransferase 3α; CDKN1B, cyclin-dependent kinase inhibitor 1B; TET2, tet methylcytosine dioxygenase 2; CREBBP, CREB binding protein; CREB, cAMP-response element binding protein; KMT2D (MLL2), histone-lysine N-methyltransferase 2D; KMT2C (MLL3), lysine N-methyltransferase 2C; BRD9, bromodomain-containing protein 9; SMARCA4, transcription activator BRG1; CHD3, chromodomain helicase DNA binding protein 3; MAPK1, mitogen-activated protein kinase 1; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CARD11, caspase recruitment domain-containing protein 11; PRKG1, cGMP-dependent protein kinase 1; NF-κB, nuclear factor-κB; NFAT, nuclear factor of activated T-cells; SDF1, stromal cell-derived factor 1; CXCL12, C-X-C motif chemokine ligand 12; Ang1, angiopoietin 1; Tie2, angiopoietin receptor; LDH, lactate dehydrogenase; G-CSF, granulocyte colony-stimulating factor; IP-10, interferon γ-induced protein 10; Jun, AP-1 transcription factor; Bcl-2, B-cell lymphoma 2; SOCS-3, suppressor of cytokine signaling-3

Key words: cutaneous T-cell lymphoma, vascular endothelial growth factors, proteomics, biomarker, antiangiogenic therapy

Contents

1. Overview on cutaneous T-cell lymphoma

Molecular biology research has contributed a great deal to advances in medical research, most notably in hematology and

oncology. Molecular mechanisms governing hematopoietic differentiation and proliferation, as well as mutations involved in hematopoietic malignancies, are now better understood (1-3).

The established guidelines for the diagnostic and clinical management of hematologic malignancies, including lymphomas, were published in 2008, under WHO coordination, and were revised in 2017 (4). T-cell lymphomas are classified into several categories, based on WHO recommendations, accessible in recent reviews (5-8). CTCLs are characterized by the recruitment of malignant T-cell clones into the skin. Mycosis fungoides (MF) represent the most common type of CTCL and account for ~50% of all primary cutaneous lymphomas, followed by Sézary syndrome. In 2018, the EORTC cutaneous lymphoma task force proposed a uniformity in classification and prognostic of these two entities using flow cytometry (9).

An important player in the pathogeny of most tumors is the vascular niche (10), responsible for increased output of growth factors, such as VEGF (vascular endothelial growth factor) and FGFb, that promote uncontrolled cell growth. An association between angiogenesis and prognostics of MF has been well established (11-13) and repeated attempts have been made to target it therapeutically (14,15). This review is focusing on molecular mechanisms and druggable molecular targets, as well as biomarker progress made in the diagnostics and prognostics of CTCLs.

2. Molecular mechanisms that drive initiation and progression of cutaneous T-cell lymphoma

Several dysregulated gene/proteins and signaling pathways have been associated with CTCLs (Fig. 1), but the exact mechanism of initiation and progression of this disorder is not yet known. Recent studies suggested that cancer testis (CT) genes are ectopically expressed in CTCLs and play an important role in carcinogenesis. These genes can sustain cell survival by inhibition of apoptosis, can promote chemo- and radio-therapy resistance and contribute to oncogenesis by targeting p53 and p21 tumor suppressor genes. Moreover, these genes can sustain aneuploidy and genomic instability by producing aberrant chromosomal translocations (16,17).

Another molecular mechanism involved in malignant transformation of CTCLs is represented by the aberrant activation of JAK3 kinase and its key down-stream effectors, STAT3 and STAT5. Therefore, IL-2, IL-4, IL-7, IL-15, and IL-21 cytokines are involved in early pathogenesis, whereas constitutive, interleukin-independent activation of the JAK3/STAT3 pathway seems to be associated with progressive and advanced disease. Aberrant activation of the JAK3/STAT signaling pathway and interleukin-independent proliferation of malignant T-cells are also related to a decreased expression and/or deregulation of function of the negative regulators SOCS-3 and SHP1. Aberrant activation of JAK3/STAT signaling pathway increases the expression of IL-5, IL-10, IL-17A, IL-17F and angiogenic factors, and sustains the resistance to treatment with histone deacetylase (HDAC) inhibitors in malignant T-cells (18).

IL-2Rgc-signaling cytokines, including IL-2, IL-4, IL-7, IL-15, and IL-21, have been associated with the pathogenesis of CTCLs (19). Recent studies suggested that IL-21 could be considered a potent antitumor agent, which increases the cytotoxicity of both natural killer (NK) and $CD8^+$ T-cells. Circulating IL-21 levels in patients with tumor MF were significantly lower than those of healthy controls and plaque MF and the IL-21 expression level decreased during tumoral-stage (20). Another study demonstrated that, in lesional skin, malignant and reactive T-cells produce IL9, a process regulated by STAT3/5. IL9-depleted mice showed a reduction of tumor growth, higher frequencies of regulatory T-cells, and activated CD4 and CD8 T lymphocytes (21). Upregulation of a chemokine receptor CCR6 and its ligand CCL20 was found in advanced CTCL cells; automatic activation of the STAT3/CCL20/CCR6 signaling seems to have an important role in CTCL lymphomagenesis and could be responsible for spreading malignant T-cells to sentinel lymph nodes, the bloodstream, and internal organs (22).

The development of blood and lymphatic vessels was associated with the progression of CTCL. Therefore, malignant T-cells produce angiogenic factors, such as podoplanin (PDPN), lymphatic vessel hyaluronan receptor-1 (LYVE-1), VEGF-C, VEGF-R3, and lymphotoxin-α (LTα), molecules involved in neoangiogenesis and neolymphoangiogenesis by promoting endothelial cell development and tube formation, mainly by stimulation of IL-6 expression (23).

The activation of CXCR4/CXCL12 axis was also associated with MF development. Moreover, administration of anti-CXCL12 and CXCR4 agents, including the anti-CXCR4 drug AMD3100 (plerixafor), the CXCL12 analog CTCE-9908, the anti-CXCL12 aptamer Nox-A12 seems to have promising effects in preclinical and clinical studies as an adjuvant antitumor therapy (24).

Epigenetic mechanisms that activate Notch signaling pathway has also been found associated with CTCL. Notch signaling is involved in cell differentiation, proliferation and stemness. Genome-wide DNA methylation analysis in MF showed a significant methylation and downregulation of the Notch-related microRNAs, especially for miR-200c and miR-124 (25).

Several studies suggested that patients with CTCL present a distinct miRNA expression profile. For example, increased expression of miR-21 and miR-155 is able to promote resistance to apoptosis and malignant proliferation and is associated with poor prognosis and aggressive behavior (19,26). In Sézary syndrome, a downregulation of the miR-22 tumor suppressor was observed, also associated with the activation of JAK3/STAT3 signaling (18). Another study demonstrated that miR-150 was downregulated only in advanced MF patients, but its expression can be restored using pan-HDACI treatment. Same results were obtained in the case of miR-16, whose expression is decreased in early stages of MF, but can also be restored by administration of vorinostat, another compound that inhibits HDACs. These results suggest that dysregulation of miRNAs by HDACs has an important role in the pathogenesis of CTCL, in both early and advanced stages, since these miRNAs are able to inhibit the expression of many oncogenes (27).

Using whole-exome sequencing, da Silva Almeida *et al* reported a distinctive pattern of somatic copy number alterations in tumor samples from patients with Sézary syndrome and other CTCLs (28). The analyses identified highly preva-

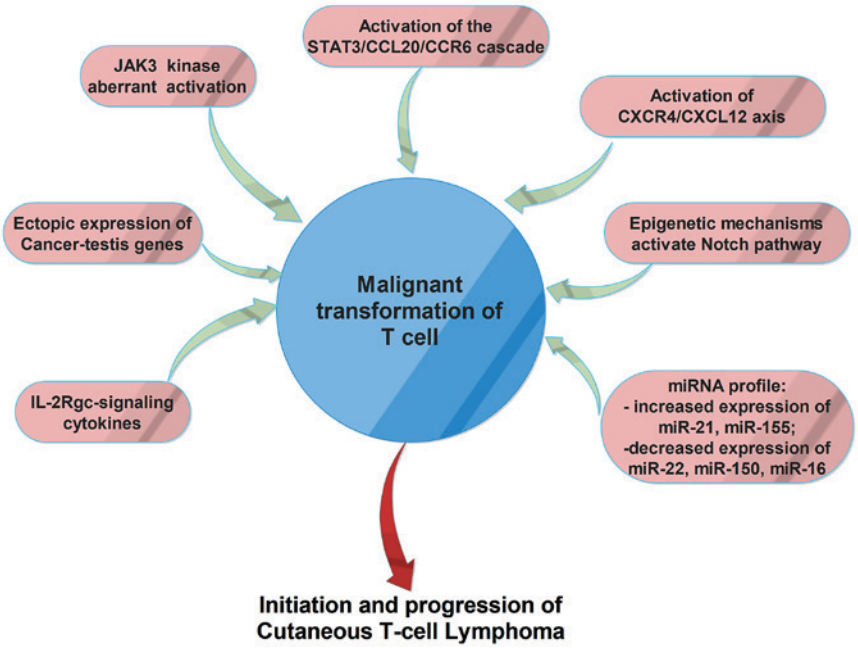

Figure 1. The main molecular mechanisms involved in malignant transformation of T-cells in cutaneous T-cell lymphomas.

lent chromosomal deletions involving the TP53, RB1, PTEN, DNMT3A and CDKN1B tumor suppressors. Somatic mutations were found in key genes involved in epigenetic regulation [TET2, CREBBP, KMT2D (MLL2), KMT2C (MLL3), BRD9, SMARCA4 and CHD3]. Signaling pathways are also affected by mutations in MAPK1, BRAF, CARD11 and PRKG1 that result in increased MAPK, NF-κB and NFAT activity upon T-cell receptor stimulation.

3. Tumor niche of cutaneous T-cell lymphoma - emphasis on vascular microenvironment

A niche is a microenvironment, both physical and functional. The physical niche is delineated by several cellular players, centered on the main resident; in this case, tumor cells. In addition to the central resident of the niche, other cellular partners contribute to create a physical or a functional scaffold, the latter mainly via soluble factors. Presently, Pubmed search using the terms 'cutaneous T-cell lymphoma vascular niche' yielded no results, although microvascularization has been previously studied in relationship with this class of tumor (12,29). Neovascularization of lymphoma can be quantified by microvessel density (MVD), which is the result of cooperation between tumor cells, proangiogenic stromal cells and infiltrating benign T lymphocytes and myeloid cells. It is used as an early marker in MF (29), but quantification reports vary among different studies due to the heterogeneity of lymphoma stroma, the range of cell surface markers used for staining and differences in scoring methodology (30). In general, MVD scores trend highest in aggressive subtypes including Burkitt's lymphoma and PTCL, compared with intermediate in DLBCL and lower in indolent follicular lymphoma (FL).

Creation of a new vascular niche in CTLCs can be argued by the emerging role of stromal cell derived factor 1 (SDF1, CXCL12) and its receptor C-X-C motif chemokine receptor 4 (CXCR4) axis in progression of MF. Signaling via this axis is known as the main regulating factor for homing of hematopoietic stem cells to the bone marrow niche (31). In MF, neoplastic T-cells express CXCR4, especially in the pretumor stage, to interact with increased levels of CXCL12, playing a critical role in MF progression (32). This axis seems to play an important role in both early and advanced stages of the disease (24).

Endothelial activation and synthesis of growth factors can be driven by another couple ligand/receptor; angiopoietin-1 (Ang1)/Tie2. In bone marrow, activation of this axis is associated with hematopoietic stem cell quiescence (33). Also, Ang1 and its co-family member Ang2 have been associated with angiogenesis. The recent study of Kawaguchi *et al* showed that circulating levels of Ang2 (not Ang1), might play a role in Sézary syndrome disease activity. In addition, expression of $Ang2^+$ cells in lesional skin of CTCL was higher than in normal skin (34).

The main factor responsible for the angiogenic switch is the family of VEGF. Members of the VEGF family: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor (PlGF), through interactions with their receptors, regulate vascular angiogenesis and lymphangiogenesis (13). These factors create positive feedback loops between endothelium and tumor cells, as well as autocrine feedback, as it has been demonstrated that acute lymphocytic leukemia and aggressive subtypes of lymphoma; peripheral T-cell lymphoma (PTCL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and primary effusion lymphoma express both VEGF and VEGFRs (35).

Regarding lymphoid vessels, there are also reports of increased formation of lymphatic vasculature and secondary lymphoid structures in CTLC. In addition to the classic factors, Lauenborg *et al* studied LTα involvement in the progression and invasion of tumor T-cells. They showed that CTCL cells express LTα *in situ*, which acts as an autocrine factor and is

driven by aberrantly activated JAK3/STAT5 pathway. LTα and LTα-induced expression of IL-6, and together with VEGF, promoted tumor angiogenesis (23). Activation of the same signaling pathway has also been correlated with IL-17A and/or IL-17F secretion that modulate oncogenic angiogenesis (36).

Malignant stroma (fibroblasts, inflammatory and infiltrated immune cells, such as monocytes and dendritic cells), provides additional angiogenic and pro-proliferative cues for tumor cells. In MF, tumor-associated macrophages were activated by stroma-produced periostin, to create a tumor niche (37). Stromal cells produce thymic stromal lymphopoietin and IL-16 that trigger T-cell recruitment to the skin (38). The stroma of MF can be highlighted by the presence of (LT)β and CCL21 (39).

Cells from tumor stroma, such as macrophages, can be targeted for destruction either by treatments aimed primarily at tumor cells, such as interferons (40), or directly, using cell-targeted treatments (in this case, macrophage-targeted) (41).

Molecular pathways associated with tumor cells and modified stroma are further targeted in biomarker research and for therapeutic purposes, as discussed further.

4. Proteomic biomarkers for diagnostic and prognostic of CTLC

An article by Humphrey *et al* (42) argues the utility of serum ribonuclease as a biomarker for leukemia diagnosis. In this paper, the authors refer to an even earlier work from the same decade (43). Since then, as the term entered in current research language, most notably in protein research, different definitions have been suggested, trying to harmonize terms and concepts.

The current widely accepted definition of a 'biomarker' was first provided by Biomarkers Definition Working Group in 2001: 'A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention' (44,45). This definition was modified in 2016 by the FDA-NIH Biomarker Working Group to 'characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions' (46).

The nature of a biomarker may vary from molecular, to a histological, imagistic or physiologic characteristic. Following advances in molecular biology technologies, molecular biomarkers can now be classified into four main types: i) Genomic biomarkers, based on the analysis of specific DNA sequences; ii) transcriptomic biomarkers, based on the analysis of RNA expression profiles; iii) proteomic biomarkers, based on the analysis of peptide/protein profiles in a wide range of biological samples from cell cultures and tissue biopsies to cerebrospinal fluid and tears; and iv) metabolomic biomarkers, based on the analysis of final- or by-products of different metabolic pathways.

Various studies emphasize the relevance of proteomics as a useful tool for biomarker identification, through minimally invasive procedures, allowing a precise approach by providing the proteomic signature of the disease. High-throughput proteomic technologies e.g., ultrasensitive microarray, are nowadays focused on discovery of specific biomarkers, expanding our knowledge regarding the mechanisms responsible for disease development, enabling early diagnostic, prognostic, monitoring and even tailored therapy of the disease (8,47-54).

Given the indolent nature of CTCLs, with majority of cases evolving over many years with a very slow progression, identification of circulating biomarkers for early diagnosis, differentiation and prognosis would be of great benefit for patients suffering of CTLC (55). Serum markers are helpful tools in determining the tumor burden in cutaneous lymphoma and thus might prove useful for disease monitoring during treatment. There is also a prognostic value that they may have for predicting the clinical course.

Circulating endothelial progenitor cells (EPC) and VEGF levels appear to correlate with tumor volumes. The phenotype $CD133^{+}CD34^{+}VEGFR\text{-}2^{+}$ EPC present in peripheral blood and lymph nodes in patients with non-Hodgkin lymphoma; the blood levels are increased in younger patients and those with aggressive lymphomas (56). It has been shown that circulating levels of the soluble interleukin-2 receptor (sIL-2R) of α-chain and lactate dehydrogenase (LDH) are significantly correlated with lymph node size, however the correlation with cutaneous clinical severe symptoms are significant only with regard to sIL-2R in erythrodermic patients. Furthermore, it has been established that tissue-based lymphoma cells express low levels of sIL-2R, whilst large-cell transformation in CTCL contributes to lowering high levels of sIL-2R in several patients. Besides sIL-2R, other two molecules-neopterin and β2-microglobulin seem to express significant high levels in serum samples from patients suffering from Sézary syndrome. Of these considered biomarkers, only sIL-2R appears to be the most sensitive; nevertheless, in terms of prognosis, only neopterin revealed a substantial significance in nonleukemic CTCL patients (57).

Circulating markers like neopterin, β2-microglobulin, sIL-2R, IL-6 and -4 have been described to be elevated in various malignancies. Studies show that increased cytoplasmic IL-4 is the sole predictor of advanced CTCL disease. Concerning the outcome of the disease (progression versus non-progression), only neopterin showed a significant prognostic value in CTCL patients (58).

The histological and molecular characteristics play a key-role in establishing the prognosis of CTLC. Various protein biomarkers useful in CTLC diagnosis have been established, comprising CD2, CD3, CD4, CD5, CD7, CD8, CD14, CD16/56, CD19, CD25, CD45, CD45RA, CD45R0. Moshkovskii *et al* analyzed the differential cytokine expressions of IL-1Ra, IL-4, G-CSF, IP-10 in serum samples of MF in the attempt to estimate the probability of an accurate diagnosis based on serum protein profiling using mass spectrometry SELDI-TOF. In their study, the authors concluded that IP-10 may be considered a candidate biomarker for the differentiation between MF and other skin conditions (59,60).

Moreover, molecules engaged in signaling pathways, regulation of cellular proliferation, and apoptosis such as Jun, Myc, c-myb, p53, STATs, Bcl-2, Fas/CD95 and SOCS-3, or involved in immunopathology such as expression of inhibitory MHC receptors (ILT2/CD85j), NK receptors (p140/KIR3DL2) and dendritic cell defects (CD40 abnormal expression) could be of significant relevance concerning CTLC prognosis (61). There

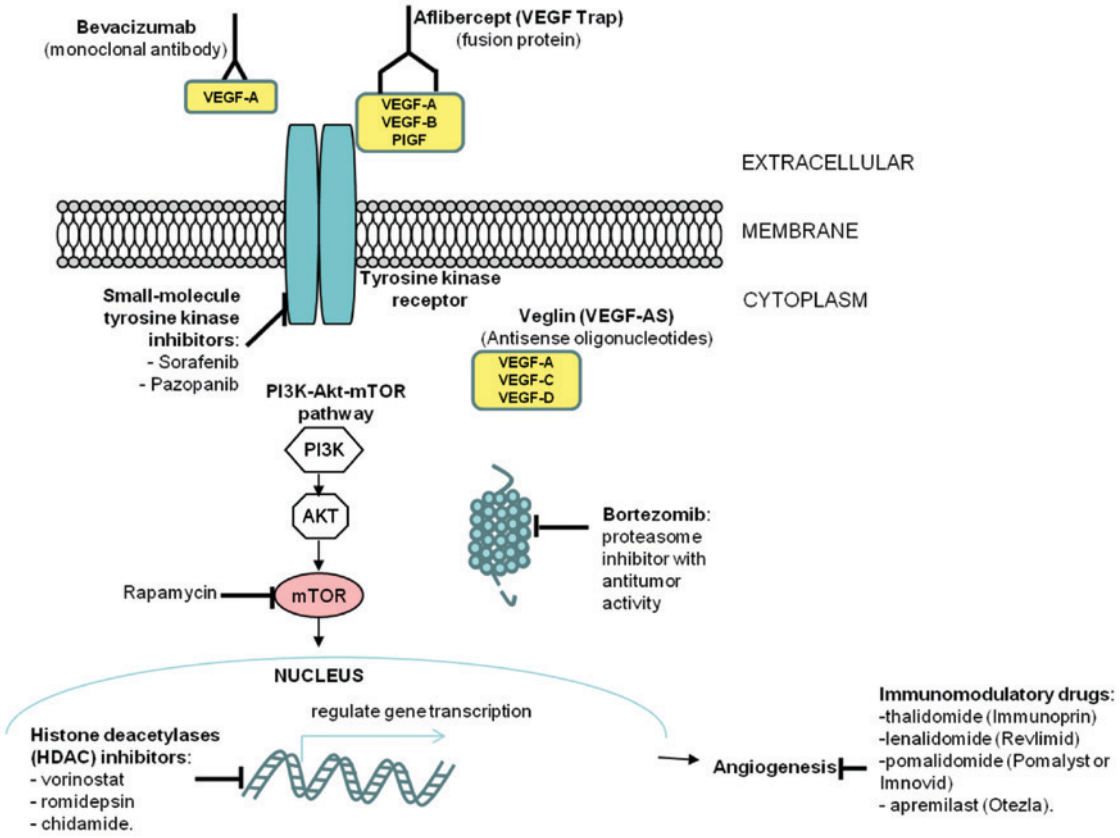

Figure 2. Targeted antiangiogenic therapy strategies in cutaneous T-cell lymphomas.

are few studies on the characterization of DCs in cancer, with implication of their expression of CD40. It is well recognized that CD40 is a co-stimulatory molecule, belonging to the tumor necrosis factor superfamily, essential in DCs activation, and suggested that CD40 expression in DCs is impaired in cancer, particularly in metastatic disease.

It has been highlighted that aberrant activation of the JAK/STAT signaling pathway was encountered in almost all T-cell lymphomas, leading to activation of pathways downstream of the T-cell receptor (TCR), co-stimulatory proteins, and/or cytokine receptors (62,63). Considering the high prevalence of CTCL, it is necessary to determine specific biomarkers in order to discriminate between more or less aggressive forms CTLC.

In this regard, future studies are needed to establish the suitable biomarkers for an accurate early diagnostic of cutaneous lymphoma. The integration of proteomics into clinical practice needs a high-throughput laboratory infrastructure, leading to the development of personalized medicine, adapting the specific biomarkers to application of cancer-type specific drug targets to individuals.

5. Molecular targets in vascular niche factors

The growing list of antiangiogenic therapies available (summarized in Fig. 2) includes:

i) Direct anti-VEGF (bevacizumab, VEGF-Trap, VEGF-antisense); due to the importance of the VEGF axis for the angiogenic process, research efforts focused on direct targeting of VEGF. The prototypic therapeutic agent is the humanized monoclonal antibody bevacizumab, which in combination with chemotherapy improves progression free-survival for patients with metastatic colorectal, renal, breast and advanced non-small cell lung cancer (64-66). Other strategies directly targeting VEGF include the use of antisense oligonucleotides against VEGF, reported to cause a partial response in one CTCL patient (14) and aflibercept (VEGF Trap), a fusion protein consisting of the extracellular domains of VEGFR receptors 1 and 2 fused to the Fc portion of human IgG. Aflibercept was reported to be well tolerated and have antitumoral activity in patients with advanced solid tumors in a phase I clinical trial (67).

ii) Immunomodulatory drugs with antiangiogenic properties; this group includes a number of anticancer agents, among which the prototype drug thalidomide (Immunoprin) (68), and its more recently developed analogues: Lenalidomide (Revlimid), pomalidomide (Pomalyst or Imnovid) and apremilast (Otezla). A phase III clinical study of lenalidomide maintenance after debulking therapy in patients with advanced CTCL revealed that lenalidomide maintenance increased progression free survival. However, these results were not statistically significant due to the reduced number of patients enrolled in the study (69,70).

iii) Metronomic chemotherapy refers to the administration of relatively low doses of medications at close regular intervals without prolonged drug-free break periods rather than the conventional 'maximum tolerated dose' (71). This approach preferentially damages endothelial cells in tumor blood vessels presumably due to a simultaneous blockade of VEGF-A blunting a key survival signal for endothelial cells,

thus selectively amplifying the endothelial cell targeting effects of chemotherapy, leading to improved subsequent killing of cancer cells (72).

iv) Other novel antiangiogenic strategies, which include: a) Mammalian target of rapamycin (mTOR) inhibitors; mTOR inhibitors have shown antiangiogenic activity by inhibiting VEGF production through HIF-1α (73,74) and mTOR has emerged a promising target for cancer therapy in both solid and hematological tumors. Primary cells from patients with CTCL or Sézary syndrome were reported to be sensitive to rapamycin (75) and the inhibition of mTOR was shown to induce apoptosis in CTCL cells (76); b) HDAC inhibitors; the first clinical data to support the use of HDAC inhibitors in CTCL came from a 2001 phase-1 trial that looked at the effect of romidepsin on a variety of cancers. The 3 patients with CTCL enrolled had partial remission, while a PTCL patient had complete remission (77). Currently, HDAC inhibitors approved for the treatment of CTCL include vorinostat; c) Proteasome inhibitors; ubiquitin-proteasome pathway inhibition in tumor cells impedes tumor growth by inducing cell cycle arrest, apoptosis and inhibiting tumor metastasis and angiogenesis. Bortezomib is a proteasome inhibitor with antitumor activity (78,79) that has several downstream effects, including activation of p53, inhibition of NF-κB and accumulation of pro-apoptotic proteins (80). Bortezomib was approved in 2003 by the FDA for the treatment of multiple myeloma and for relapsed or refractory mantle cell lymphoma (81,82) and several reports and clinical trials reveal that it can also be used for the treatment of solid tumors, alone or in combination (83-85). Bortezomib has shown promising results in patients with relapsed or refractory CTCL (86-88).

6. Conclusion

Neoangiogenesis plays potentially important pathogenic roles in CTLC initiation and prognostic, by stimulating homing of tumor cells and generation of pro-proliferative soluble cues. The main signaling pathway involved in autocrine stimulation of proliferation and survival of lymphoma tumor cells is VEGF-VEGF receptor axis, although other axes, described in homing studies (CXCR4/CXCL12) or signaling pathways (JAK3/STAT5) associated with hematopoietic development were recently associated with clinical and fundamental studies of CTLC. Proteomic studies are useful to highlight more members of these signaling pathways that are modified in the lesions or serum of patients and that may be used in prognostic or therapy follow-up. These studies can also highlight novel molecular therapy targets, possibly some with higher specificity for characterized subsets of patients, in the framework of personalized medicine.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CT, IDP, AME, AAGG, EC, SM, LA, LN and RA contributed to the gathering of the data, writing the manuscript and revising it critically for an important intellectual content. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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