Advances in lymphoma biomarkers research based on proteomics technology (Review)

QIBEI LIU*, JIANMIN LING*, ZHAO LI and LINTAO BI

Department of Hematology, China-Japan Union Hospital of Jilin University, Changchun, Jilin 130033, P.R. China

Received January 16, 2025; Accepted May 30, 2025

DOI: 10.3892/or.2025.8941

Abstract. Lymphoma is a common malignancy characterized by diverse pathological types and marked heterogeneity. Distinct subtypes of lymphomas are markedly different in their clinical manifestations, treatment approaches and prognostic outcomes. With the rapid development of molecular biology techniques, antitumor research has stepped into an era of precision medicine. Biomarkers, with high sensitivity and specificity, are expected to function in early diagnosis, targeted treatment and prognostic estimation for cancer and enhance the survival rate and life quality of patients. In this regard, proteomics technology, with the capability to systematically identify and quantify the dynamic protein alterations in tissues or cells, thereby facilitating the discovery of novel tumor potential candidates, has attracted significant scientific attention. The present article aimed to review most up-to-date research progress of lymphoma-related biomarkers discovered based on proteomics technology, focusing on the potential application of these markers in the diagnosis, therapy and prognosis of each lymphoma subtype, and discuss the role proteomics may serve in future development of lymphoma research and clinical practice.

Contents

Correspondence to: Dr Lintao Bi, Department of Hematology, China-Japan Union Hospital of Jilin University, 126 Xiantai Street, Changchun, Jilin 130033, P.R. China
E-mail: bilt@jlu.edu.cn

*Contributed equally

Key words: lymphoma, proteomics, biomarkers, diagnosis, therapy, prognosis

1. Introduction

Lymphoma, a group of common malignant tumors arising from the lymphohematopoietic system, is broadly classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). HL accounts for ~10% of all lymphoma cases, demonstrating a low incidence of recurrence and a favorable cure rate, while NHL constitutes ~90% of lymphomas (1). According to the 2022 Global Cancer Observatory, lymphoma accounted for 635,858 new cases and 273,412 mortalities worldwide, with NHL incidence showing a consistent upward trend (2). Given the variety of lymphoma subtypes, Fig. 1 presents a schematic diagram of the lymphoma classification framework employed in the present review.

Indolent lymphoma subtypes frequently present with an insidious onset and hidden symptoms during their early stages. Thus, patients lacking palpable lymph node enlargement are prone to misdiagnosis. While immunochemotherapy-based combination therapy has increased the survival probability of patients with lymphoma, a considerable proportion of patients fail to respond to existing treatments (3). Primary resistance and cumulative toxicities remain critical barriers of antitumor treatments. Moreover, in the wake of tumor progression, the therapeutic difficulty increases and the prognosis deteriorates. In addition, heterogeneous biological characteristics of different lymphoma subtypes pose a challenge for prognostic assessment. Therefore, a pressing demand for diagnostic indicators, therapeutic targets and prognostic predictors with high sensitivity and specificity for lymphoma exists.

Advances in molecular biology have shifted cancer research toward precision medicine, where biomarkers, defined as objectively measurable indicators of normal biological processes, pathological states or therapeutic responses (4), serves a central role. Proteins, as the primary functional molecules in biological systems, offer distinct advantages over nucleic acid-based biomarkers by more comprehensively reflecting pathophysiological processes, including post-translational modifications, protein interactions and microenvironmental influences (5).

Proteomics is a science that investigates the existence and function of proteins within cells and tissues (6). This technology generates clinically actionable insights in disease research by detecting the variations of proteins under physiological or pathological conditions and decoding tumor-specific mechanisms inaccessible to genomes and transcriptomes (Fig. 2).

For instance, differentially expressed proteins (DEPs) between tumor tissues and benign tissues hold significant potential as biological targets for diagnosis and therapy.

The core technology platform of proteomics is liquid chromatography-tandem mass spectrometry (LC-MS), which enables high-throughput and precise identification, quantification and characterization of proteins (7). This field primarily encompasses three key methodological components: Protein separation using two-dimensional gel electrophoresis, protein identification via MS, and final bioinformatic analysis for functional annotation and data integration. Currently, modern proteomic workflows employ diverse quantification strategies: isobaric tagging techniques including tandem mass tag and isobaric tags for relative and absolute quantitation facilitate multiplexed analysis of up to 18 samples with high sensitivity (8,9), while label-free approaches offer unlimited sample comparisons and reduced expenditure at the expense of lower stability (10). For large-scale studies, data-independent acquisition (DIA) methods can provide robust reproducibility but rely on advanced computational pipelines (11). These techniques are systematically compared in Table I.

2. Proteomic advances in different types of lymphoma

HL. HL predominantly derived from germinal center B cells (3) and is classified into nodular lymphocyte-predominant HL and classic HL (CHL), with CHL constituting >90% of HL diagnoses (12,13) and pathognomonically defined by the presence of Hodgkin and Reed-Sternberg (HRS) cells in the tumor microenvironment (TME) (13). Relapse/refractory (R/R) disease develops in ~20% of patients with CHL, while the vast majority recover after first-line chemotherapy such as ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) (12).

Therapeutic biomarkers. Although HL exhibits a relatively low overall incidence, CHL represents a frequent cancer in the pediatric and adolescent populations (14). Despite achieving favorable cure rates in pediatric patients with CHL, the intensive use of highly genotoxic chemotherapeutics is associated with significant treatment-related morbidity and mortality (14,15), which necessitates the development of safer therapeutic strategies. Consequently, biomarker-targeted therapy has emerged as an optimal solution to mitigate toxicity while maintaining efficacy. For instance, in clinical trials, Pembrolizumab, a PD1 inhibitor, and Brentuximab vedotin, a CD30 inhibitor, yielded an overall response rate of respectively 69 and 75% in patients with R/R CHL (16,17).

Scientists continue to pursue novel pathogenic factors in HL, such as autocrine lymphotoxin-alpha (LTA) in HRS cell, which can constitutively activates NF-κB and JAK-STAT signaling pathways (18). Also, Segges *et al* (19) investigated celastrol, an HSP90 inhibitor, in both KMH2 (celastrol-sensitive) and L428 (Celastrol-resistant) HL cells and observed suppression of MAPK/ERK signaling in KMH2 cells and upregulation of Hsp27 in L428 cells.

Prognostic biomarkers. Given the distinct epidemiology of HL, identifying robust prognostic biomarkers for pediatric and adolescent patients with CHL is critical for optimizing risk-adapted clinical management. To address this need, two plasma proteomic profiles comparing relapsed and non-relapsed pediatric CHL cohorts were conducted by Repetto *et al* (14,20), where five of the DEPs (AAT, FGA, FGB, C4BPA and CLU) were specifically validated. In a parallel study, Honoré *et al* (21) performed a comparative proteomic analysis between pretherapy tumor biopsies from ABVD-responsive and refractory patients with CHL, reporting that the pathological activation of the CXCR4 pathway accounted for the failure of ABVD. CXCR4 inhibitors such as Plerixafor, which is clinically used for treating NHL and multiple myeloma, may serve as a supplementary therapeutic approach for patients with ABVD-insensitive CHL.

Diagnostic biomarkers. Proteomics can also provide several diagnostic biomarkers for HL, for which researchers often consider inflammatory and immune-related proteins that interact with HRS cells as candidates.

In 2011, chemical proteomics was used to compare CHL tissues with reactive lymphoid hyperplasia (RLH) by Kischel *et al* (22), who reported the increased expression of certain extracellular matrix proteins in CHL tissues. Subsequently, using glycoproteomics, Powlesland *et al* (23) identified the glycoproteins CD98hc, ICAM-1 and DEC-205 as carriers of CD15, a characteristic marker of CHL. In 2021, Gholiha *et al* (24) carried out a proteomic analysis similar to Kischel *et al* (22), using the Proximity Ligation Assay with attention to the plasma protein despite tumor lysates, and reported increased levels of PD-L1 alongside several PD-L1-associated proteins in both tissues and plasma.

Epstein-Barr virus (EBV) was first isolated from an African patient with Burkitt lymphoma (BL) (25) and was the first oncogenic virus causally linked to human cancers. Amongst the four subtypes of CHL [mixed cellularity (MC), nodular sclerosis, lymphocyte-depleted (LD) and lymphocyte-rich] (12), it has been reported that the EBV positivity rate is 70% in MC and 95% in LD (26).

Since it has been shown that EBV infection may affect the survival of elderly patients with HL (27,28), EBV-associated proteins may offer novel targets for proteomic interrogation in HL. For instance, by proteome-wide microarray technology, Sarathkumara *et al* (29) constructed antibody profiles of patients with EBV-positive CHL in European and East Asian populations and found that LMP1-IgG was markedly increased in both cohorts, compared with patients with EBV-negative CHL. Liu *et al* (30) performed a similar experiment with samples obtained from patients in the UK and BdRF1 (VCAp40)-IgG and BZLF1 (Zta)-IgG have been identified as serological markers for EBV-positive CHL. All the details of experimental findings are presented in Table II, while Fig. 3 provides a schematic representation of the proposed functional relationships and interactions among candidate proteins identified through part of HL proteomic experiments.

NHL

B cell NHL (B-NHL). B-NHL encompasses a heterogeneous group of malignancies characterized by distinct molecular pathogenesis and clinical trajectories, representing 85-90% of NHL cases (31).

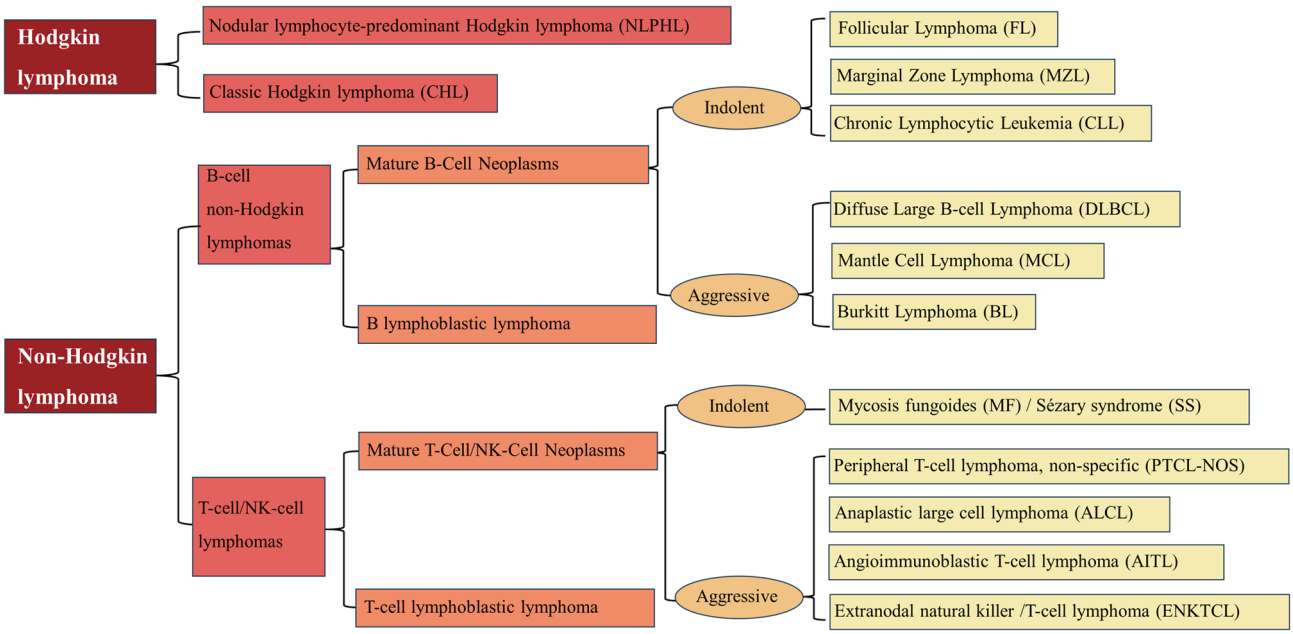

Figure 1. Schematic representation of the classification framework for lymphomas.

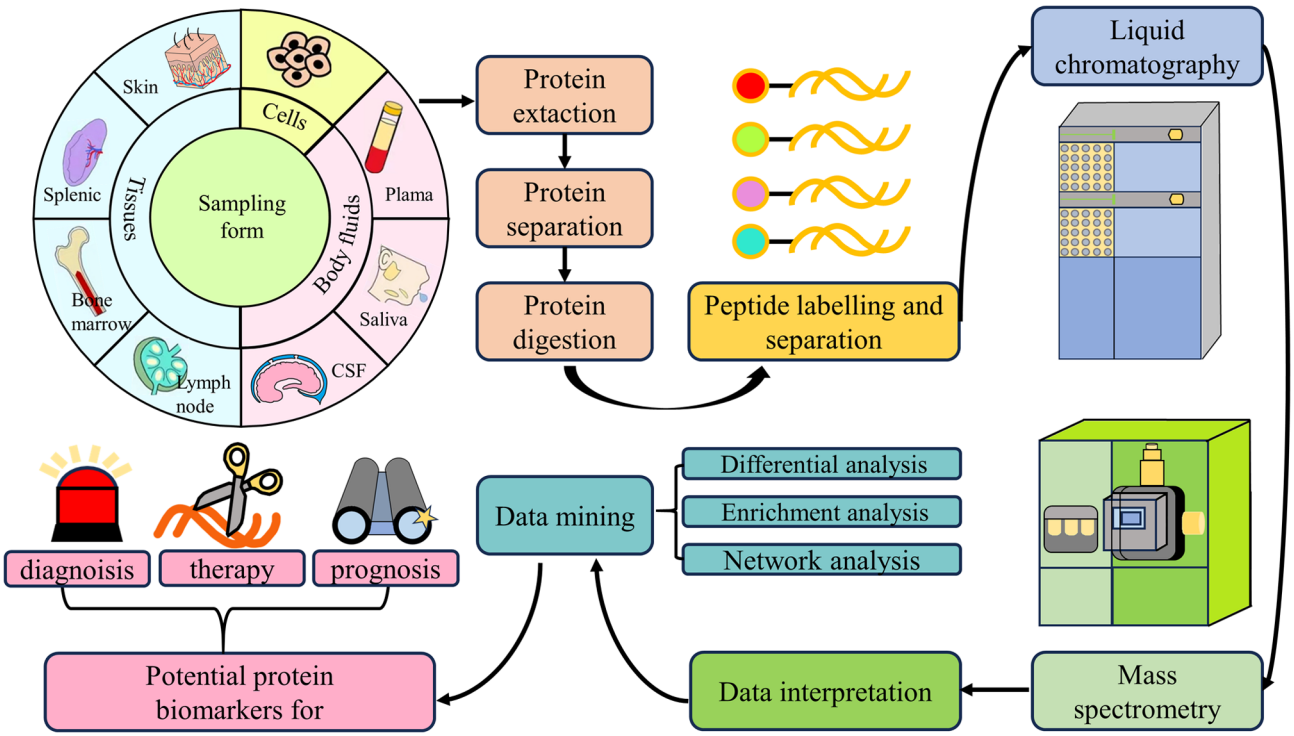

Figure 2. Workflow and methodological pipeline for clinical proteomics analysis. CSF, Cerebrospinal Fluid, a key biofluid used in clinical proteomics studies.

Diffuse large B cell lymphoma (DLBCL). DLBCL is the most common B-NHL (32), constituting ~35% of NHL cases with an estimated global annual incidence of 150,000 cases (33). According to the cellular origin, DLBCL can be classified into three subtypes, namely germinal center B cell-like (GCB) DLBCL, activated B cell-like (ABC) DLBCL and unclassified DLBCL (34). Based on immunophenotype, ABC DLBCL can also be categorized as non-germinal center B-cell like (non-GCB) DLBCL (35), which demonstrates inferior treatment outcomes compared with GCB DLBCL following R-CHOP treatment (36). While R-CHOP treatment, the incorporation of anti-CD20 monoclonal antibodies rituximab with CHOP-based chemotherapy (Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisone), can cure 60% of patients with DLBCL, those with R/R disease exhibit a median overall survival (OS) of only 6 months (37). Currently, no novel targeted agents have demonstrated sufficient clinical efficacy against DLBCL.

Table I. Common proteomic technologies for lymphoma analysis.

Technique	Advantages	Disadvantages	Validation approaches
iTRAQ/TMT	Suitable for multiple sample types. Good sensitivity and repeatability.	Only 8-18 samples can be labeled at one time. High cost of labeling reagents.	Western blotting ELISA Immunohistochemistry PRM/MRM Flow Cytometry qPCR Functional validation
SILAC	100% labelling efficiency. Real-time and authenticity. Available for minimal proteins.	Limitations exist for sample types other than cells. Long experimental period.	
Label-free	No labelling required. Relatively low cost.	Quantitative accuracy is low and affected by mass spectrometry stability. Complex data analysis and poor reproducibility.	
DIA/SWATH	Suitable for large-scale studies. Recognizing low abundance proteins. Good accuracy and repeatability.	Data processing complexity. Higher costs and equipment requirements.	

iTRAQ, isobaric tags for relative and absolute quantitation; TMT, tandem mass tag; SILAC, Stable Isotope Labeling by Amino acids in Cell culture; ELISA, Enzyme-linked immunosorbent assay; PRM, Parallel reaction monitoring; MRM, Multiple reaction monitoring; qPCR, quantitative polymerase chain reaction ; DIA, data-independent acquisition; SWATH, sequential window acquisition of all theoretical mass spectra.

Diagnostic biomarkers. In 2019, two proteomic experiments were conducted by Gao *et al* (38) and van der Meeren *et al* (39), respectively comparing the proteomic profiles of ABC DLBCL with RLH and non-GCB DLBCL with GCB DLBCL. In 2021, Reinders *et al* (40) performed proteomic analysis on formalin-fixed paraffin-embedded tumor tissues from the three subtypes of DLBCL and reported that CD44, PTN1 and IGHM were upregulated in ABC DLBCL, while TOM22 showed higher expression in GCB DLBCL.

Therapeutic biomarkers. Recognizing DEPs between CHOP-sensitive and CHOP-resistant DLBCL helps to seek out new therapeutic targets and biomarkers indicating a high risk of relapse for R/R DLBCL, as demonstrated by Fornecker *et al* (41). Furthermore, Zhou *et al* (42) reported that the knock down of KLHL6 can upregulate its downstream molecule NOTCH2 and lead to DLBCL resistance to R-CHOP.

McCrury *et al* (43) demonstrated that elevated NEK2 expression serves as a predictor of poor prognosis in DLBCL and developed a novel NEK2 inhibitor, NBI-961, which is currently in preclinical development. Bram Ednersson *et al* (44), using quantitative proteomics of a large group of patients with DLBCL, identified the upregulation of CD64 in non-GCB DLBCL and the increase of IRF8 in GCB DLBCL. Moreover, enrichment analyses showed that most DEPs were associated with the TME and immune system regulation, suggesting potential therapeutic strategies for non-GCB DLBCL.

CD37 is a transmembrane protein highly expressed on mature B cells. Elfrink *et al* (45) reported increased expression of IRF8 in nuclear extracts from CD37+ DLBCL compared with CD37- DLBCL, suggesting that IRF8 acts as a transcriptional regulator for CD37. A Phase II study has demonstrated that the anti-CD37 antibody-drug naratuximab emtansine (Debiopharm) in combination with rituximab markedly improved objective response rate (ORR;44.7%) and complete response rate (31.6%) in patients with R/R DLBCL, with a manageable safety profile (46).

Prognostic biomarkers. Recent advances in proteomic-numerous have uncovered a variety of prognostically relevant proteins to DLBCL. Gao *et al* (47) and Lou *et al* (48) both conducted large-cohort proteomic profiling of patients with DLBCL and respectively established TCL1 and TIMP1 as predictors of survival. Through interactome analysis, Jiang *et al* (49) demonstrated that high HGAL expression attenuates DLBCL tumor cell motility by binding to certain cytoskeletal regulators. Furthermore, a series of comparative proteomic experiments have delineated molecular differences between patients with DLBCL and healthy subjects (50), R-CHOP resistant and R-CHOP sensitive DLBCL (51,52), GCB DLBCL and non-GCB DLBCL (53), CD5+DLBCL and CD5-DLBCL (54) and DLBCL with higher survival and with lower survival (55) (Table III).

Mantle cell lymphoma (MCL). MCL exhibits a clinical spectrum from indolent to highly aggressive and is responsible for ~7% of NHL cases (56). Despite substantial advances in cancer therapy such as chimeric antigen receptor-T cells (CAR-T) treatment, MCL remains largely incurable.

Research has focused on identifying new therapeutic targets related to known oncoproteins overexpressing in MCL, such as SOX11, which was shown to upregulate PDGFA thus promote angiogenesis (57) and SEA1/2, the activating enzyme in SUMO pathway (58). Notably, SEA inhibitor TAK-981 can

Table II. HL-related biomarkers based on proteomics technology.

First author/s, year	Sample nature	Protein biomarker	Type of biomarker	Proteomic technology	Number of sample	(Refs.)
Von Hoff *et al*, 2019	Cell lines	LTA	Therapeutic	/	L1236 cell	(18)
Segges *et al*, 2018	Cell lines	RAS, ERK1, ERK2, p90RSK1, Hsp70	Therapeutic	Label-free	L428 cell and KMH2 cell	(19)
Repetto *et al*, 2018	Plasma	AAT, FGA, FGB	Prognostic	/	15 relapsing HL, 14 non-relapsing HL	(14)
Repetto *et al*, 2022	Plasma	C3BPA, CLU	Prognostic	Label-free	14 relapsing HL, 28 non-relapsing HL	(20)
Honoré *et al*, 2022	Tissue	GNAI2, GNB1, RALB, PAK2, CRK, GNAQ, ARPC5	Prognostic	Label-free	15 treatment-refractory CHL, 21 treatment-sensitive CHL	(21)
Kischel *et al*, 2011	Tissue	VCAN, FBLN1, POSTN, S100A8	Diagnostic	Chemical proteomics	4 HL, 3 reactive lymphoid hyperplasia	(22)
Powlesland *et al*, 2011	Cell lines	CD98hc, ICAM-1, DEC-205	Diagnostic	Glyproteomics	L-428, KMH-2, L-1236, L-540, HDLM-2 and U-HO1 cell lines	(23)
Gholiha *et al*, 2021	Tissue and plasma	PD-L1, IL-6, CCL17,CCL3, IL13, MMP12, TNFRS4, LAG3	Diagnostic	Immune-proteomics	27 CHL tissues vs. 30 reactive lymph node lysates; plasma from 26 CHL patients and 27 healthy controls	(24)
Sarathkumara *et al*, 2024	Plasma	LMP1-IgG, TK-IgG, BALF2-IgG, BDLF3-IgG, BBLF1-IgG	Diagnostic	EBV proteome microarray	35 EBV+ CHL, 92 EBV- CHL, 60 controls	(29)
Liu *et al*, 2020	Serum	BdRF1-IgG, Zta-IgG	Diagnostic	EBV proteome microarray	139 EBV+ CHL, 70 EBV- CHL, 141 controls	(30)

HL, Hodgkin lymphoma; CHL, classical Hodgkin lymphoma.

significantly reduce the proteins involved in transcription such as MAX, MGA,ARID4A/B and PML in MCL (58).

Lokhande *et al* (59) investigated the TME in MCL and proposed CD47, IDO1 and CTLA-4 as potential biotargets for MCL presenting with high levels of T cell infiltration, while GITR, TIGIT, LAG 3, PD-L1 and PD-L2 may be promising targets for MCL with low levels of T cell infiltration.

BL. BL is a highly aggressive B-NHL and primarily occurs in children, which comprises three clinicopathological subtypes: Sporadic BL (sBL), immunodeficiency-associated BL and endemic BL (eBL), the latter exhibiting near-ubiquitous EBV infection.

EBV-encoded proteins can promote lymphomagenesis in BL. Recent proteomic researches have revealed that Zta binds the cellular protein NFATcs, suppressing its expression to circumvent cytotoxic and apoptosis (60). EBV can overcome replication stress in B lymphocytes through the regulation of replisome-associated proteins such as ZFP91, ZNF503 and ZC3H18 (61). Additionally, El-Mallawany *et al* (62) initiated the first proteomic comparative report on cell lines from

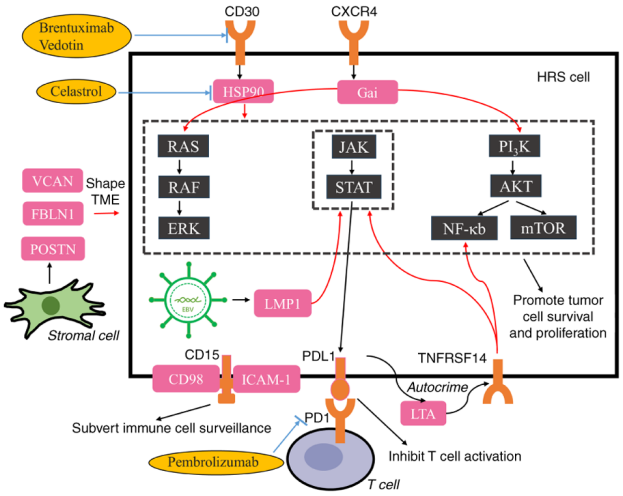

Figure 3. Schematic representation of the functions and interactions of some candidate proteins related to HL proteomic experiments. HL, Hodgkin lymphoma; HRS cell, Hodgkin-Reed-Sternberg cell; TME, tumor microenvironment

EBV+/- sBL, EBV+ eBL and EB- normal B lymphocytes and observed several co-upregulated proteins (TUBB2C, UCHL1 and HSP90AB1) in both eBL and sBL as well as protein elevated specifically in eBL (C1QBP and ENO1) and sBL (PCNA and SLC3A2).

Currently, BL demonstrates sensitivity to intensive chemoimmunotherapy. However, patients with R/R BL, which accounts for 20-40% of cases, continue to face a poor prognosis (46). Emerging precision therapeutic regimens, such as histone deacetylase inhibitors, may offer promising therapeutic potential.

Chronic lymphocytin leukemia (CLL)/small lymphocytic lymphoma (SLL). CLL/SLL are indolent B-cell neoplasms characterized by a CD19+/CD5+/CE23+ immunophenotype and account for 7-10% of NHL (63). Despite differences in anatomic distribution, SLL and CLL are considered a single disease entity. Epidemiologically, CLL predominantly affects older males, with an annual incidence in the Western world of 4.2/100,000 per year (64).

CLL is uniquely identifiable among B-NHL due to its distinctive immunophenotype of peripheral blood, rendering extensive proteomic biomarker studies less prioritized for CLL diagnosis. However, Ikhlef *et al* (65) highlighted the role of tumor-associated macrophage-derived extracellular vesicle (EVs) in CLL-B cells *in vitro*, reducing apoptosis, increasing proliferation and generating BTK inhibitor (BTKi) resistance. Furthermore, EVs transported various oncogenic proteins that mediated the upregulation of IGFBP2 in CLL-B cells.

Therapeutic biomarkers. BTK, a pivotal node in the B-cell receptor (BCR) signaling cascade, is a therapeutic target for CLL. However, clinical limitations persist, particularly in individuals with BTK mutations. Consequently, recent efforts have focused on identifying alternative biological targets within the BCR axis. Aslan *et al* (66) performed proteomic profiling of BTK-mutant compared with BTK-wild-type CLL at the baseline level and demonstrated PCK upregulation in both cohorts after a course of pirtobrutinib (a BTKi) treatment. Griffen *et al* (67) identified LYN, MEF2C and NUMB as prognostic biomarkers through comparative proteomics of CLL compared with normal B cells of BTKi-treated patients with CLL. These candidates may function as BTK-cooperative targets, with HSP90 demonstrating a synergistic potential by stabilizing ROR1, a tumor-promoting protein in CLL, as reported by Liu *et al* (68). Among ROR1-targeted therapies, two distinct strategies have emerged with promising but differential activity profiles: Zilovertamab vedotin, a ROR1-directed antibody-drug conjugate (ADC), was evaluated in a first-in-human Phase I dose-escalation study (69). The trial demonstrated encouraging preliminary activity in MCL (ORR=46.7%) and DLBCL (ORR=60%); however, no significant antitumor response was observed in the CLL cohort, underscoring potential disease-specific variations in therapeutic response. By contrast, the anti-ROR1 monoclonal antibody cirmtuzumab showed clinically meaningful activity in CLL patients during a Phase I trial, with 17 of 22 evaluable patients (77.3%) achieving stable disease (70). As well as suppressing ROR1 signaling, cirmtuzumab attenuated stemness-related gene expression in CLL patients, further validating ROR1 as a viable therapeutic target. Notably, Merck Sharp & Dohme is poised to initiate a Phase III trial for DLBCL in December 2025. If successful, this could position ROR1-ADC as the first approved ROR1-targeted therapy, marking a significant milestone in the field.

Beyond the hyperactivation of the BCR signaling pathway, RNA splicing dysregulation is also a hallmark of molecular aberration in CLL. Johnston *et al* (71) identified the independent overexpression of RNA spliceosome components and other potential therapeutic targets such as CKAP4 in CLL. Additionally, Bagacean *et al* (72) demonstrated the prognostic capability of RNA splice proteins in a clinical cohort study and Wu *et al* (73) further indicated that the dysregulation is linked to overexpression of METTL3.

Furthermore, Subramaniam *et al* (74) conducted a comparative quantitative proteomic profiling of neutrophils from Uropathogenic Escherichia coli (UPEC)-infected CLL mouse models compared with UPEC-challenged wild-type controls, demonstrating that CLL were more susceptible to UPEC, which could be explained by neutrophil toxic dysfunction and migratory function impairment. Therapeutic restoration of CD62L and CXCR4 may help to mitigate bacterial infection risk in CLL. In parallel, Ecker *et al* (75) proposed another therapeutic option to activate the DNA damage response (DDR) and apoptosis by inhibiting DUSP1/6 to relieve its suppression on the MAPK pathway.

Prognostic biomarkers. Immunoglobulin heavy chain variable region (IGHV) mutation status remains the gold standard prognostic biomarker in CLL, since CLL patients with unmutated IGHV (UM-CLL) have a markedly shorter OS compared with those with mutated IGHV (M-CLL) (64). However, the IGHV mutation status does not alter with CLL progression. Therefore, studies have tried to decipher the protein mechanisms by which IGHV mutation status drives clinical heterogeneity. In this regard, Beckmann *et al* (76) reported that MARCKS exhibits both high expression and hyperphosphorylation in UM-CLL cells, while and Stachelscheid *et al* (77) identified that proto-oncoprotein TCL1A is highly expressed and CD20 is downregulated in these cells.

Table III. DLBCL-related biomarkers based on proteomics technology.

First author/s, year	Sample nature	Protein biomarker	Type of biomarker	Proteomic technology	Number of sample	(Refs.)
Gao *et al*, 2019	Tissue	HSP90AB1, GNA13, LAMB2, LAMA5, YWHAZ	Diagnostic, therapy	iTRAQ	7 ABC DLBCL, 8 control	(38)
van der Meeren *et al*, 2019	Cell lines	RPL23, GLMN	Diagnostic	SILAC	7 non-GCB, 5 GCB DLBCL	(39)
Reinders *et al*, 2020	Tissue	CD44, PTN1, IGHM, TOM22	Diagnostic	SWATH	18ABC, 4 unclassified, and 20 GBC DLBCL	(40)
Fornecker *et al*, 2019	Tissue	HK3, IDO1, CXCL13, S100A4,-8,-9, -11, CD79B	Therapeutic	Label-free	8 chemorefractory and 12 chemosensitive DLBCL	(41)
Zhou *et al*, 2023	Cell lines	NOTCH2, KLHL6	Therapeutic	Unbiased proteomic	9 DLBCL cell lines	(42)
McCrury *et al*, 2024	Cell lines	NEK2	Therapeutic	TMT and Phospho-Proteomics	3 DLBCL cell lines	(43)
Bram Ednersson *et al*, 2021	Tissue	CD64, CD85A, IFIT2, GBP1, MLKL, MNDA, IRF8, SWAP70, WEE1	Therapeutic	TMT	202 adult DLBCL	(44)
Elfrink *et al*, 2022	Cell lines	IRF8	Therapeutic	Unbiased proteomic	CD37+, CD37- DLBCL cell lines	(45)
Gao *et al*, 2020	Tissue	TCL1	Prognostic	iTRAQ	137 DLBCL	(47)
Lou *et al*, 2023	Plasma	TIMP1	Prognostic	DIA	147 DLBCL	(48)
Jiang *et al*, 2021	Cell lines	HGAL	Prognostic	Unbiased proteomic	GCB DLBCL cell lines	(49)
Zhu *et al*, 2020	Plasma	SAA, CRP	Prognostic	DIA	19 DLBCL, 18 healthy control	(50)
Ludvigsen *et al*, 2023	Tissue, plasma	SAA, DKK3, FCN3	Prognostic	Label-free	53 treatment-sensitive and 11 relapsing; 24 treatment-sensitive and 7 relapsing	(51)
Feng *et al*, 2020	Serum	CA1	Prognostic	TMT	81 chemo-sensitive, 31 chemo-resistant	(52)
Kwiecińska *et al*, 2018	Tissue	Hsp90, BiP/Grp 78, cyclin B2	Prognostic	/	3 non-GCB, 3 GCB DLBCL	(53)
Hiratsuka *et al*, 2023	Tissue	DNAJB1, DDX3X	Prognostic	Label-free	5 CD5+DLBCL, 6 CD5-DLBCL	(54)
Zhu *et al*,	Tissue	MPO	Prognostic	SWATH	52 DLBCL	(55)

DLBCL, diffuse large B cell lymphoma; GCB DLBCL, germinal center B cell-like DLBCL; ABC DLBCL, activated B cell-like DLBCL; iTRAQ, isobaric tags for relative and absolute quantitation; DIA, data-independent acquisition; TMT, tandem mass tag; SILAC, Stable Isotope Labeling by Amino acids in Cell culture; SWATH, sequential window acquisition of all theoretical mass spectra.

Meanwhile, efforts to circumvent the expense and difficulty of genetic testing have yielded novel prognostic indicators independent from IGHV. For instance, Griffen *et al* (78) investigated the expression pattern of DDR in CLL and Saberi Hosnijeh *et al* (79) performed a proteomic analysis on baseline sera sampling from patients with CLL being treated with chemoimmunotherapy. Furthermore, Lu *et al* (80) proposed a novel concept of CLL cell proliferation drive (CLL-PD) as a CLL prognostic determinant and confirmed that high expression of mTOR-MYC-OXPHOS pathway-associated proteins were positively associated with the intensity of CLL-PD. Furthermore, Griffen *et al* (67) and van Dijk *et al* (81) both validated the prognostic significance of H3K27Me3 and respectively proposed several other potential prognostic markers.

Given the wait-and-watch strategy for CLL, the aforementioned prognostic markers focus on evaluating therapeutic responses. Hence, there are few markers that exist for asymptomatic CLL. To fill this gap, by comparing the proteomic profilings of CLL with time-to-first treatment thresholds ≤24 and >24 months, Hengeveld (82) concluded that THEMIS2 may be an IGHV mutation independent predictor of early progression.

A detailed account of CLL-related biomarkers identified through proteomics technology is provided in Table IV.

Follicular lymphoma (FL). FL, one of the most prevalent indolent NHL, accounts for ~35% of NHL cases and up to 70% of inert lymphomas in Western populations (83). FL typically follows a relapsing-remitting clinical course (84). To overcome the therapeutic and prognostic evaluation bottlenecks in FL, high-resolution proteomic approaches are revolutionizing therapeutic and prognostic biomarkers discovery for FL.

Prognostic biomarkers. Histological transformation (HT) to aggressive DLBCL occurs in 10-70% of FL cases, representing the primary cause of FL mortality. Notably, most patients with FL remain asymptomatic until HT development. Consequently, a large proportion of FL diagnoses are established at advanced stages with a median diagnosis age of 65 years (83). These clinical realities underscore a critical need for reliable prognostic biomarkers to enable early intervention and improve survival outcomes for FL.

In this context, comparative proteomic analyses of FL with or without subsequent HT have identified candidate protein biomarkers associated with disease progression. Specifically, Enemark *et al* (85) demonstrated upregulated apoptotic proteins such as CASP3 and Monrad *et al* (86) and Ludvigsen *et al* (87) reported enhanced expression of glycolytic enzymes such as ALDOA and GAPDH in FL with HT. Notably, PFK158, a novel glycolysis inhibitor has entered clinical evaluation for its antitumor efficacy in FL.

Recent proteomic advances have markedly enhanced the identification of prognostic biomarkers in FL. In 2023, Deng *et al* (88) performed comparative profiling of patients with FL and stratified cohorts into long-lasting remission and early progression within 2 years (POD24), revealing the increased expression of GLUT1, immunosuppressive markers and related chemokines along with the decreased expression of inflammatory cytokines in POD24 FL. In 2024, Radtke *et al* (89) performed single-cell proteomic analysis on lymphoid follicles from healthy individuals and patients with FL and showed that an increased proportion of DC-SIGN+ cells and the existence of IRF4+ tumor B lymphocytes were associated with early relapse and low survival in FL, respectively.

Therapeutic biomarkers. Radiotherapy and chemotherapy combined with immunotherapy such as rituximab are the mainstream treatments for FL (83). However, current therapies fail to prevent relapse in most patients with FL and early progression after initial treatment is associated with shorter survival (90). However, emerging therapies do not consistently meet current safety standards, but suggest that the selection of therapeutic targets is shifting towards protein-based biomarkers. In 2021, a large-scale proteomic comparison between FL and normal B cells was performed using the total protein approach by Duś-Szachniewicz *et al* (91), demonstrating that DEPs were mostly enriched in BCR signaling pathways and cellular adhesion molecules interactions. These findings, along with other key proteomics-based discoveries in FL, are summarized in Table V.

Marginal zone lymphoma (MZL). Accounting for ~7% of NHL, MZL represents the second most common indolent lymphoma. MZL originates from B lymphocytes in the marginal zone and is classified into three subtypes based on anatomical involvement: extranodal MZL (EMZL), splenic MZL (SMZL) and nodal MZL (NMZL). While the tumor progresses slowly, with a median OS >10 years, the advanced-stage disease remains incurable, similar to FL (92).

EZML. EMZL accounts for 70% of MZL (92), which arises in diverse mucosal tissues, such as the stomach, lungs, ocular adnexa (OA) and skin (93), rendering highly heterogeneous (95). Therefore, current research often concentrates on tissue-specific EMZL variants.

OA-EMZL constitutes the most frequent subtype of OA lymphoma (94). Studies during 2022 and 2023 by Shi *et al* (95-97) validated the diagnostic potential of IgM and DNAJC9 and the prognostic potential of PCNA, MCM6 and MCM4 in OA-EMZL.

Additionally, it is common for EMZL to develop from chronic inflammation, including autoimmune disorders such as primary Sjögren's syndrome (PSS) and infections such as *Helicobacter pylori* (HP) (98,99). Protein markers enabling the differentiation between lymphoid hyperplasia and malignant transformation will help to reduce unnecessary interventions.

PSS is an autoimmune disorder characterized by lymphocyte hyperplasia and exocrine gland dysfunction (100). PSS is associated with a 1,000-fold increased risk of parotid lymphoma compared with the general population (101); however, the underlying mechanisms remain poorly understood. Jazzar *et al* (101) and Cui *et al* (102) reported a series of diagnostic protein markers capable of distinguishing patients with PSS from healthy individuals and patients with PSS with EMZL from patients with PSS without lymphoma.

Additionally, gastric EMZL (GML) is the most common subtype of digestive MZL, presenting HP infection in most of these cases (103). There is a close association between HP eradication and a favorable remission rate in EMZL (99). By exploring the molecular mechanisms by which HP induces GML, candidate biomarkers can be detected for timely diagnosis and effective remedies:

Table IV. CLL-related biomarkers based on proteomics technology.

First author/s, year	Sample nature	Protein biomarker	Type of biomarker	Proteomic technology	Number of sample	(Refs.)
Ikhlef *et al*, 2024	Blood	IGFBP2, CD40, P53, BCL2	Diagnostic, therapeutic, prognostic	/	CLL-B-cell	(65)
Aslan *et al*, 2024	Blood	FAS, CD29, CAV1, MCL-1, BBC3, JNK, UBQLN4, CDKN2A, MIF, VDAC1, BAK, CCNE1, LCK, SGK3,TAZ, OCT4, PAICS, LCN2, CD20, HLADQA1, TFR1, PCK	Therapeutic	Reverse Phase Protein Array	11 BTK-mutated CLL, 7 BTK-wide-type CLL	(66)
Griffen *et al*, 2022	Blood and bone marrow	CHEK1, GAB2, IGFBP2, S100A4,WEE1, ZAP90, LYN, MEF2C, NUMB	Therapeutic	Reverse Phase Protein Array	871 CLL	(67)
Liu *et al*, 2020	Cell lines	ROR1	Therapeutic	iTRAQ	CLL cells	(68)
Ecker *et al*, 2023	Cell lines	DUSP6, DUSP1	Therapeutic	Phospho-proteome	B cells from healthy donors and CLL patients	(75)
Johnston *et al*, 2018	Blood	CKAP4, PIGR, TMCC3, CD75, LAX1, CLEC17A, ATP2B4, WEE1, HMOX1, HMOX2, HDAC7, INPP5F	Therapeutic	/	B cells from healthy donors and CLL patients	(71)
Wu *et al*, 2023	Blood	METTL3	Therapeutic	TMT	B cells from healthy donors and CLL patients	(73)
Subramaniam *et al*, 2021	Blood	MPO, CP, CXCR4, CD62L	Therapeutic	/	CLL mice	(74)
Beckmann *et al*, 2021	Blood	MARCKS, AK1, COX5B	Prognostic	Phospho-proteome	B cells from CLL patients	(76)
Stachelscheid *et al*, 2023	Blood	TCL1A, CDC20	Prognostic	/	B cells from healthy donors and CLL patients	(77)
Griffen *et al*, 2023	Blood and bone marrow	CHEK1, CHEK2. pT68, DDB1, PDCD1, RAD51, SSBP2, CHEK1	Prognostic	Reverse Phase Protein Array	727 frozen, 68 fresh, 743 blood, 52 bone marrow	(78)

Table IV. Continued.

First author/s, year	Sample nature	Protein biomarker	Type of biomarker	Proteomic technology	Number of sample	(Refs.)
		pS296, RPA32, VCP			samples from CLL patients, 5 controls	
Hosnijeh *et al*, 2020	Serum	SPINT1, LY9	Prognostic	Proximity Extension Assay	51 CLL	(79)
Lu *et al*, 2021	Blood	NME1, MCM4, PAICS, VDAC1, HSPD1	Prognostic	/	46 CLL	(80)
Griffen *et al*, 2022	Blood and bone marrow	H3K27Me3, MCL1, BCL2L11, NCSTN, SGK3, HSPD1, VTCN1, TRAP1, SOD1, TAZ	Prognostic	Reverse Phase Protein Array	871 CLL	(67)
van Dijk *et al*, 2022	Blood	EZH2, HDAC6, H3K27Me3	Prognostic	Single-cell proteomics	547 CLL	(81)
Hengeveld *et al*, 2023	Blood	THEMIS2	Prognostic	TMT	40 CLL with TTFT ≤24, 40 CLL with TTFT >24	(82)

CLL, chronic lymphocytin leukemia; iTRAQ, isobaric tags for relative and absolute quantitation; TMT, tandem mass tag; TTFT, time-to-first treatment.

In 2020, Zou *et al* (103) infected BGC823 human gastric cancer cells and GES-1 human healthy gastric epithelial cells with HP 26695 and HP isolated from GML, respectively, and conducted proteomics comparison between HP 26695-infected BGC823 and GML originated HP infected-BGC823. GML-related DEPs and GML-specific DEPs were subsequently identified, with the former referring to DEPs associated with GML-isolated HP infection and the latter referring to proteins that were only associated with GML-isolated HP infection but did not differentially express or were not expressed after HP 26695 infection. Most GML-specific DEPs served roles in cancer pathways.

SMZL. SMZL constitutes 20% of all MZL cases and ~25% of patients present asymptomatically at initial diagnosis, but the majority of patients have favorable outcomes, except for 10% of cases progress to DLBCL through HT (92).

Few proteomic studies focus on SMZL pathogenesis. Notably, in 2022, Tang *et al* (104) employed CITE-seq technology to delineate two specific regulatory T cell (Treg) subgroups in SMZL and deduced that patients with increased levels of CD161+ Tregs had an improved prognosis, while the opposite was true for patients with abundant CD26+ Tregs. Moreover, the activation of the IL2/STAT5 pathway contributes to the induction of CD26+ Tregs, which can be reversed by inhibiting STAT5.

NMZL. NMZL is extremely rare and no NMZL-specific protein biomarkers have been identified to date. All experimental findings about MZL are comprehensively detailed in Table VI.

T cell lymphoma. T cell lymphoma accounts for 10-15% of NHL cases and is highly aggressive and heterogeneous. Despite the research progress on aggressive B-NHLs, reports on T cell lymphomas lags behind. Although the CHOP regimen is used for treating T-cell lymphoma, the 5-year OS is only 25-35% (105).

Peripheral T cell lymphoma, non-specific (PTCL-NOS). PTCL-NOS, the most prevalent and molecularly heterogeneous PTCL subtype, is diagnosed through the exclusion of other defined T cell lymphomas.

Despite its clinical significance, proteomic characterization of PTCL-NOS remains limited. A landmark 2018 study by Ludvigsen *et al* (106) conducted comprehensive proteomic profiling of pretreatment biopsies through three comparative analyses: PTCL-NOS compared with non-neoplastic lymphoid tissues, PTCL-NOS with poor OS compared with PTCL-NOS with superior OS and PTCL-NOS with chemotherapy-sensitive and survival >2 years compared with PTCL-NOS with primary refractory and survival <100 days. This study showed that a high abundance of ENO1 associated with a poor outcome in PTCL-NOS.

Table V. FL-related biomarkers based on proteomics technology.

First author/s, year	Sample nature	Protein biomarker	Type of biomarker	Proteomic technology	Number of sample	(Refs.)
Enemark *et al*, 2023	Tissue	CASP3, MCL1, BAX, BCL-xL, BCL-Rambo	Prognostic	Label-free	20 FL with HT, 34 FL without HT	(85)
Monrad *et al*, 2020	Tissue	ALDOA, GAPDH	Prognostic	/	5 FL without HT, 7 FL with HT, 6 secondary DLBCL, 9 *de novo* DLBCL	(86)
Deng *et al*, 2023	Cell lines	GLUT1, PD-1, PD-L1, CD206, CD163, IL-10, TGFβ, CCL17, CCL22, CCL5, CXCL5, TNF-α, IFN-γ, IL-12	Prognostic	TMT	FL cell lines	(88)
Radtke *et al*, 2024	Tissue	DC-SIGN, IRF4	Prognostic	Single-cell proteomics	FL with early relapse, controls	(89)
Duś-Szachniewicz *et al*, 2021	Cell lines	LYN, CD79B, VAV1, ICAM1, PIK3CA, ITGAV	Therapeutic	/	15 FL, 14 controls	(91)

FL, follicular lymphoma; HT, histological transformation; TMT, tandem mass tag.

Anaplastic large cell lymphoma (ALCL). ALCL, a CD30-positive subtype of T cell lymphoma, accounts for ~3% of adult NHL (107) and 10-20% of pediatric lymphomas (108). A majority of ALCL cases undergo a t(2;5)(p23;q35) translocation, which results in the expression of nucleophosmin-anaplastic lymphoma kinase (NPM-ALK), a tyrosine kinase (109).

In ALK-positive ALCL, drug addiction emerges following resistance to ALK tyrosine kinase inhibitors. This phenomenon is mechanistically driven by aberrant STAT1 activation, which triggers a tumor suppressive gene expression program upon drug withdrawal, leading to toxic hyperactivation of oncogenic signaling pathways, as noted by Rajan *et al* (110). Furthermore, Lovisa *et al* (111) demonstrated high expression levels of HSP90AA1, SPP1/OPN and TNC in plasmatic circulating small EVs from pediatric patients with ALCL compared with healthy donors. Moreover, Hu *et al* (112) showed that ALK upregulated PFKFB3 via its downstream transcription factor STAT3 in ALCL and ultimately resulted in the promotion of metabolic reprogramming of tumor cells. Thus PFKFB3 inhibitors can potentially overcome drug resistance in patients with TKi-resistant ALCL with an ALK mutation.

Angioimmunoblastic T cell lymphoma (AITL). AITL, deriving from mature T follicular helper cells, is relatively uncommon with a 5-year OS rate of 32-44% (113).

Furthermore, a recent study distinguished AITL from myeloproliferative neoplasms (MPN) (114). The two diseases develop from different pathogenetic mechanisms and the combination of the disease may result in a poorer patient prognosis. Histomorphometry cannot be used to detect AITL with or without MPN and there are currently no effective diagnostic markers. Holst *et al* (114) demonstrated the upregulation of DNAJA2 and downregulation of IDH2 and CS in MPN-AITL.

Extranodal natural killer/T cell lymphoma (ENKTCL). ENKTCL is a rare malignancy derived from peripheral NK/T cells, primarily affecting extranodal sites. Although the condition is relatively rare in Western populations, it exhibits a markedly higher prevalence in South America and Asia (115). EBV is the main causative agent of ENKTCL, although the precise pathogenic mechanisms remain poorly understood (116,117).

Extranodal nasal NK/T cell lymphoma (ENKTL), the most common type of ENKTCL, often presents with symptoms mimicking ENT disorders, leading to frequent misdiagnosis and delayed treatment. Consequently, there is a pressing demand for ENKTL diagnostic markers. Li *et al* (118) demonstrated the overexpression of HRG in the cerebrospinal fluid samples from patients with ENKTL patients compared with patients without ENKTL, highlighting its potential diagnostic utility.

Patients with ENKTCL can experience chemotherapy resistance and relapse, with a median survival of ~4 months post-relapse (119). Due to the limited availability of prognostic markers, Zhou (120) conducted serum proteomic analysis on 32 patients with advanced ENKTCL,

Table VI. MZL-related biomarkers based on proteomics technology.

First author/s, year	Sample nature	Protein biomarker	Type of biomarker	Proteomic technology	Number of sample	(Refs.)
Shi *et al*, 2023	Serum	IgM	Diagnostic	DIA	28 EMZL, 10 DLBCL, 10 IOI, 10 RLH	(95)
Shi *et al*, 2022	Tissue	DNAJC9	Diagnostic	TMT	40 EMZL, 12 IOI, 6 RLH, 13 controls	(96)
Zhu *et al*, 2023	Tissue	PCNA, MCM6, MCM4	Prognostic	TMT	6 EMZL with distant recurrence, 21 EMZL without distant recurrence	(97)
Jazzar *et al*, 2018	Saliva	S100A8, S100A9	Diagnostic	/	2 SS, 2 SS at risk of developing MALT, 2 controls	(101)
Cui *et al*, 2017	Saliva and tissue	CFL1, ENO1, RGI2	Diagnostic	/	6 pSS, 6 pSS/MALT, 6 controls	(102)
Zou *et al*, 2020	Cell lines	MCM6, RPN2, ILF2, RPL35A, EIF3B *etc*.	Diagnostic	TMT	BGC823 cell and 26695 cell	(103)
Tang *et al*, 2022	Tissue	CD161,CD26	Prognostic	Single-cell proteomics	24 SMZL, 12 controls	(104)

MZL, marginal zone lymphoma; DIA, data-independent acquisition; EMZL, extranodal MZL; DLBCL, diffuse large B cell lymphoma; IOI, idiopathic orbital inflammation; RLH, reactive lymphoid hyperplasia; pSS, primary Sjögren's syndrome; MALT, mucosa-associated lymphoid tissue; SMZL, splenic MZL; TMT, tandem mass tag.

categorizing them into responders and non-responders based on predefined criteria. The findings showed upregulation of S100A9 and ORM1 in the non-responding group, suggesting their potential role in predicting treatment outcomes. Further insights into ENKTCL pathogenesis and treatment response were provided by Gong *et al* (121), who investigated proteomic differences in cerebrospinal fluid from patients with NKTCL with ethmoidal sinus metastasis before and after cytarabine-based chemotherapy. The authors reported upregulation of CPE and downregulation of IGFBP2 post-treatment, indicating potential biomarkers for therapeutic monitoring. Additionally, Qiu *et al* (122) reported elevated levels of YWHAE in asparaginase-based chemoresistant patients with ENKTL compared with sensitive patients, further underscoring the role of proteomic alterations in chemoresistance.

Mycosis fugnoides (MF)/Sézary syndrome (SS). MF/SS represents the most prevalent subtypes of cutaneous T-cell lymphoma (CTCL), sharing significant overlap in clinical and biological characteristics. MF accounts for ~60% of CTCL (123) and typically follows an indolent course, presenting with early manifestations of cutaneous plaques and lymph node and visceral metastases at an advanced stage. By contrast, SS, comprising ~5% of CTCL (124), is rarer and may arise *de novo* or evolve from MF. SS is characterized by a more aggressive clinical course and poorer prognosis. Given the atypical clinical and histological manifestations along with low tumor burden in the early phases of MF/SS, the existing means of diagnosis are relatively ineffective. However, recent proteomic studies have identified novel diagnostic markers by comparing MF tissues with benign inflammatory diseases or healthy controls (125-127). In addition, Lemchak *et al* (128) identified DEPs in early-stage biopsies from patients with invasive compared with non-invasive MF, offering potential prognostic biomarkers for disease progression. All experimental findings specific to MF/SS are detailed in Table VII.

3. Conclusions and future prospective

Proteomics, a core discipline of systems biology, is undergoing a paradigm shift from traditional protein identification to single-cell resolution and multi-dimensional detection. The integration of machine learning, particularly in biomarker screening, protein-protein interaction network construction and functional prediction, has enhanced the efficiency and accuracy of proteomic data analysis. Notably, biomarker group-based diagnostic strategies have emerged as a primary focus in clinical proteomics due to their superior sensitivity and specificity compared with single biomarkers.

However, proteomics research faces several challenges: i) Sample variability caused by tissue heterogeneity, protein degradation and contamination compromises result reliability; ii) the wide dynamic range of protein abundance leads to signal masking, where high-abundance proteins obscure critical low-abundance regulatory proteins; iii) dynamic protein expression influenced by microenvironment and cellular

Table VII. MF/SS-related biomarkers based on proteomics technology.

First author/s, year	Sample nature	Protein biomarker	Type of biomarker	Proteomic technology	Number of sample	(Refs.)
Techner *et al*, 2023	Tissue	KLK6, PI3, HMOX1, CSTB	Diagnostic	Proximity extension assay	39 MF, 21 healthy control	(125)
Qureshi *et al*, 2023	Stratum corneum	GSDMC, PSMD6, PDIA4, ERP29, CD44	Diagnostic	DIA	28 MF and normal stratum	(126)
Leng *et al*, 2022	Tissue	DYNC1I2, CD14, COL18A1, CRABP2	Diagnostic	DIA	4 early-stage, 10 advanced-stage MF,11 healthy control	(127)
Lemchak *et al*, 2018	Tissue	PARP1, HSAP1L, THSPA1A, DDX17, LAP2α	Prognostic	Global proteomic	4 aggressive, 4 non-aggressive	(128)

MF, mycosis fugnoides; SS, Sézary syndrome; DIA, data-independent acquisition.

states increases experimental standardization complexity; and iv) despite advances, current mass spectrometry technologies still lack sufficient sensitivity, resolution and throughput for comprehensive analysis, particularly in large-scale post-translational modification studies.

Meanwhile, a substantial proportion of candidate biomarkers remain confined to preclinical investigation or early-phase clinical trials. The translation from discovery to clinical application is a complex, costly and lengthy process, being hindered by: i) The need for multicenter, large-scale clinical validation to assess biomarker robustness across populations and disease stages; ii) stringent regulatory requirements, including analytical validation, clinical utility verification and clinical validity confirmation; and iii) additional constraints such as assay standardization, cost-effectiveness analysis and ethical considerations.

Nevertheless, the integration of single-cell proteomics and multi-omics technologies offers promising avenues for accelerating the discovery and validation of lymphoma-specific biomarkers. This multi-omics approach overcomes the limitations of single-omics studies through data complementarity, enhancing result reliability. Such integrated strategies will facilitate the clinical translation of proteomics research, ultimately enabling precise molecular classification, personalized treatment and prognostic assessment in lymphoma management.

Acknowledgements

Not applicable.

Funding

This work was supported by the Natural Science Foundation of Jilin [grant numbers YDZJ202201ZYTS117].

Availability of data and materials

Not applicable.

Authors' contributions

QL and JL authored or reviewed drafts of the paper, provided figures and tables, and approved the final draft. ZL provided tables and helped with proofreading of draft. LB prepared tables and approved the final draft. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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.

References

1. Ansell SM: Hodgkin lymphoma: 2025 update on diagnosis, risk-stratification, and management. Am J Hematol 99: 2367-2378, 2024.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
3. Klein C, Jamois C and Nielsen T: Anti-CD20 treatment for B-cell malignancies: Current status and future directions. Expert Opin Biol Ther 21: 161-181, 2021.
4. Califf RM: Biomarker definitions and their applications. Exp Biol Med (Maywood) 243: 213-221, 2018.
5. Hristova VA and Chan DW: Cancer biomarker discovery and translation: Proteomics and beyond. Expert Rev Proteomics 16: 93-103, 2019.
6. Müllner S, Neumann T and Lottspeich F: Proteomics-a new way for drug target discovery. Arzneimittelforschung 48: 93-95, 1998.

7. Cox J and Mann M: Quantitative, High-resolution proteomics for Data-driven systems biology. Annu Rev Biochem 80: 273-299, 2011.
8. Li J, Cai Z, Bomgarden RD, Pike I, Kuhn K, Rogers JC, Roberts TM, Gygi SP and Paulo JA: TMTpro-18plex: The expanded and complete set of TMTpro reagents for sample multiplexing. J Proteome Res 20: 2964-2972, 2021.
9. Thompson A, Schäfer J, Kuhn K, Kienle S, Schwarz J, Schmidt G, Neumann T, Johnstone R, Mohammed AK and Hamon C: Tandem mass tags: A novel quantification strategy for comparative analysis of complex protein mixtures by MS/MS. Anal Chem 75: 1895-1904, 2003.
10. Neilson KA, Ali NA, Muralidharan S, Mirzaei M, Mariani M, Assadourian G, Lee A, van Sluyter SC and Haynes PA: Less label, more free: Approaches in Label-free quantitative mass spectrometry. Proteomics 11: 535-553, 2011.
11. Collins BC, Hunter CL, Liu Y, Schilling B, Rosenberger G, Bader SL, Chan DW, Gibson BW, Gingras AC, Held JM, *et al*: Multi-laboratory assessment of reproducibility, qualitative and quantitative performance of SWATH-mass spectrometry. Nat Commun 8: 291, 2017.
12. Yung L and Linch D: Hodgkin's lymphoma. Lancet 361: 943-951, 2003.
13. The guidelines for diagnosis and treatment of Hodgkin lymphoma in China (2022). Zhonghua Xue Ye Xue Za Zhi 43: 705-715, 2022 (In Chinese).
14. Repetto O, Mussolin L, Elia C, Martina L, Bianchi M, Buffardi S, Sala A, Burnelli R, Mascarin M and De Re V: Proteomic identification of plasma biomarkers in children and adolescents with recurrent hodgkin lymphoma. J Cancer 9: 4650-4658, 2018.
15. Brice P, de Kerviler E and Friedberg JW: Classical hodgkin lymphoma. Lancet 398: 1518-1527, 2021.
16. Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, Radford J, Ribrag V, Molin D, Vassilakopoulos TP, *et al*: Phase II study of the efficacy and safety of pembrolizumab for Relapsed/refractory classic hodgkin lymphoma. J Clin Oncol 35: 2125-2132, 2017.
17. Younes A, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, Sievers EL and Forero-Torres A: Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med 363: 1812-1821, 2010.
18. von Hoff L, Kärgel E, Franke V, McShane E, Schulz-Beiss KW, Patone G, Schleussner N, Kolesnichenko M, Hübner N, Daumke O, *et al*: Autocrine LTA signaling drives NF-κB and JAK-STAT activity and myeloid gene expression in Hodgkin lymphoma. Blood 133: 1489-1494, 2019.
19. Segges P, Corrêa S, Du Rocher B, Vera-Lozada G, Krsticevic F, Arce D, Sternberg C, Abdelhay E and Hassan R: Targeting hodgkin and Reed-sternberg cells with an inhibitor of Heat-shock protein 90: Molecular pathways of response and potential mechanisms of resistance. Int J Mol Sci 19: 836, 2018.
20. Repetto O, Caggiari L, De Zorzi M, Elia C, Mussolin L, Buffardi S, Pillon M, Muggeo P, Casini T, Steffan A, *et al*: Quantitative plasma proteomics to identify candidate biomarkers of relapse in Pediatric/adolescent hodgkin lymphoma. Int J Mol Sci 23: 9911, 2022.
21. Honoré B, Andersen MD, Wilken D, Kamper P, d'Amore F, Hamilton-Dutoit S and Ludvigsen M: Classic hodgkin lymphoma refractory for ABVD treatment is characterized by pathologically activated signal transduction pathways as revealed by proteomic profiling. Cancers (Basel) 14: 247, 2022.
22. Kischel P, Waltregny D, Greffe Y, Mazzucchelli G, De Pauw E, de Leval L and Castronovo V: Identification of stromal proteins overexpressed in nodular sclerosis Hodgkin lymphoma. Proteome Sci 9: 63, 2011.
23. Powlesland AS, Barrio MM, Mordoh J, Hitchen PG, Dell A, Drickamer K and Taylor ME: Glycoproteomic characterization of carriers of the CD15/Lewisx epitope on Hodgkin's Reed-Sternberg cells. BMC Biochem 12: 13, 2011.
24. Gholiha AR, Hollander P, Löf L, Larsson A, Hashemi J, Ulfstedt JM, Molin D, Amini RM, Freyhult E, Kamali-Moghaddam M and Enblad G: Immune-proteome profiling in classical hodgkin lymphoma tumor diagnostic tissue. Cancers (Basel) 14: 9, 2021.
25. Epstein MA, Achong BG and Barr YM: Virus particles in cultured lymphoblasts from burkitt's lymphoma. Lancet 1: 702-703, 1964.
26. Thompson MP and Kurzrock R: Epstein-Barr virus and cancer. Clin Cancer Res 10: 803-821, 2004.
27. Myriam BD, Sonia Z, Hanene S, Teheni L and Mounir T: Prognostic significance of Epstein-Barr virus (EBV) infection in Hodgkin lymphoma patients. J Infect Chemother 23: 121-130, 2017.
28. Ludvigsen M, Kamper P, Hamilton-Dutroit SJ, Bendix K, Møller MB, d'Amore FA and Honoré B: Relationship of intratumoural protein expression patterns to age and Epstein-Barr virus status in classical Hodgkin lymphoma. Eur J Haematol 95: 137-149, 2015.
29. Sarathkumara YD, Xian RR, Liu Z, Yu KJ, Chan JKC, Kwong YL, Lam TH, Liang R, Chiu B, Xu J, *et al*: A proteome-wide analysis unveils a core Epstein-barr virus antibody signature of classic Hodgkin lymphoma across ethnically diverse populations. Int J Cancer 155: 1476-1486, 2024.
30. Liu Z, Jarrett RF, Hjalgrim H, Proietti C, Chang ET, Smedby KE, Yu KJ, Lake A, Troy S, McAulay KA, *et al*: Evaluation of the antibody response to the EBV proteome in EBV-associated classical Hodgkin lymphoma. Int J Cancer 147: 608-618, 2020.
31. Silkenstedt E, Salles G, Campo E and Dreyling M: B-cell Non-hodgkin lymphomas. Lancet 403: 1791-1807, 2024.
32. Martelli M, Ferreri AJ, Agostinelli C, Di Rocco A, Pfreundschuh M and Pileri SA: Diffuse large B-cell lymphoma. Crit Rev Oncol Hematol 87: 146-171, 2013.
33. Susanibar-Adaniya S and Barta SK: 2021 Update on Diffuse large B cell lymphoma: A review of current data and potential applications on risk stratification and management. Am J Hematol 96: 617-629, 2021.
34. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD and Jaffe ES: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127: 2375-2390, 2016.
35. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, Müller-Hermelink HK, Campo E, Braziel RM, Jaffe ES, *et al*: Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103: 275-282, 2004.
36. Rosenwald A and Staudt LM: Gene expression profiling of diffuse large B-cell lymphoma. Leuk Lymphoma 44 (Suppl 3): S41-S47, 2003.
37. Roschewski M, Phelan JD and Wilson WH: Molecular classification and treatment of diffuse Large B-cell lymphoma and primary mediastinal B-cell lymphoma. Cancer J 26: 195-205, 2020.
38. Gao HX, Nuerlan A, Abulajiang G, Cui WL, Xue J, Sang W, Li SJ, Niu J, Ma ZP, Zhang W and Li XX: Quantitative proteomics analysis of differentially expressed proteins in activated B-cell-like diffuse large B-cell lymphoma using quantitative proteomics. Pathol Res Pract 215: 152528, 2019.
39. van der Meeren LE, Kluiver J, Rutgers B, Alsagoor Y, Kluin PM, van den Berg A and Visser L: A super-SILAC based proteomics analysis of diffuse large B-cell lymphoma-NOS patient samples to identify new proteins that discriminate GCB and non-GCB lymphomas. PLoS One 14: e0223260, 2019.
40. Reinders J, Altenbuchinger M, Limm K, Schwarzfischer P, Scheidt T, Strasser L, Richter J, Szczepanowski M, Huber CG, Klapper W, *et al*: Platform independent protein-based cell-of-origin subtyping of diffuse large B-cell lymphoma in formalin-fixed paraffin-embedded tissue. Sci Rep 10: 7876, 2020.
41. Fornecker LM, Muller L, Bertrand F, Paul N, Pichot A, Herbrecht R, Chenard MP, Mauvieux L, Vallat L, Bahram S, *et al*: Multi-omics dataset to decipher the complexity of drug resistance in diffuse large B-cell lymphoma. Sci Rep 9: 895, 2019.
42. Zhou N, Choi J, Grothusen G, Kim BJ, Ren D, Cao Z, Liu Y, Li Q, Inamdar A, Beer T, *et al*: DLBCL-associated NOTCH2 mutations escape Ubiquitin-dependent degradation and promote chemoresistance. Blood 142: 973-988, 2023.
43. McCrury M, Swafford K, Shuttleworth SL, Mehdi SH, Acharya B, Saha D, Naceanceno K, Byrum SD, Storey AJ, Xu YZ, *et al*: Bifunctional inhibitor reveals NEK2 as a therapeutic target and regulator of oncogenic pathways in lymphoma. Mol Cancer Ther 23: 316-329, 2024.
44. Bram Ednersson S, Stern M, Fagman H, Nilsson-Ehle H, Hasselblom S, Thorsell A and Andersson PO: Proteomic analysis in diffuse large B-cell lymphoma identifies dysregulated tumor microenvironment proteins in non-GCB/ABC subtype patients. Leuk Lymphoma 62: 2360-2373, 2021.
45. Elfrink S, Ter Beest M, Janssen L, Baltissen MP, Jansen P, Kenyon AN, Steen RM, de Windt D, Hagemann PM, Hess C, *et al*: IRF8 is a transcriptional activator of CD37 expression in diffuse large B-cell lymphoma. Blood Adv 6: 2254-2266, 2022.

46. Levy MY, Grudeva-Popova Z, Trneny M, Jurczak W, Pylypenko H, Jagadeesh D, Andre M, Nasta S, Rechavi-Robinson D, Toffanin S, *et al*: Safety and efficacy of Cd37-Targeting naratuximab emtansine plus rituximab in diffuse large B-cell lymphoma and other Non-hodgkin's B-cell Lymphomas-A phase 2 study. Hematological Oncol 39: 18-22, 2021.
47. Gao HX, Li SJ, Niu J, Ma ZP, Nuerlan A, Xue J, Wang MB, Cui WL, Abulajiang G, Sang W, *et al*: TCL1 as a hub protein associated with the PI3K/AKT signaling pathway in diffuse large B-cell lymphoma based on proteomics methods. Pathol Res Pract 216: 152799, 2020.
48. Lou N, Wang G, Wang Y, Xu M, Zhou Y, Tan Q, Zhong Q, Zhang L, Zhang X, Liu S, *et al*: Proteomics identifies circulating TIMP-1 as a prognostic biomarker for diffuse Large B-Cell lymphoma. Mol Cell Proteomics 22: 100625, 2023.
49. Jiang X, Lu X, Gentles AJ, Zhao D, Wander SA, Zhang Y, Natkunam Y, Slingerland J, Reis IM, Rabinovich B, *et al*: HGAL inhibits lymphoma dissemination by interacting with multiple cytoskeletal proteins. Blood Adv 5: 5072-5085, 2021.
50. Zhu T, Zhu Y, Xuan Y, Gao H, Cai X, Piersma SR, Pham TV, Schelfhorst T, Haas R, Bijnsdorp IV, *et al*: DPHL: A DIA Pan-human protein mass spectrometry library for robust biomarker discovery. Genomics Proteomics Bioinformatics 18: 104-119, 2020.
51. Ludvigsen M, Campbell AJ, Enemark MB, Hybel TE, Karjalainen-Lindsberg ML, Beiske K, Bjerre M, Pedersen LM, Holte H, Leppä S, *et al*: Proteomics uncovers molecular features for relapse risk stratification in patients with diffuse large B-cell lymphoma. Blood Cancer J 13: 161, 2023.
52. Feng Y, Zhong M, Tang Y, Liu X, Liu Y, Wang L and Zhou H: The role and underlying mechanism of exosomal CA1 in chemotherapy resistance in diffuse large B cell lymphoma. Mol Ther Nucleic Acids 21: 452-463, 2020.
53. Kwiecińska A, Porwit A, Souchelnytskyi N, Kaufeldt A, Larsson C, Bajalica-Lagercrantz S and Souchelnytskyi S: Proteomic profiling of diffuse large B-cell lymphomas. Pathobiology 85: 211-219, 2018.
54. Hiratsuka T, Ito S, Sakai R, Yokose T, Endo T, Daigo Y, Miyagi Y and Tsuruyama T: Proteome analysis of CD5-positive diffuse large B cell lymphoma FFPE tissue reveals downregulation of DDX3X, DNAJB1, and B cell receptor signaling pathway proteins including BTK and Immunoglobulins. Clin Proteomics 20: 36, 2023.
55. Zhu Y, Weiss T, Zhang Q, Sun R, Wang B, Yi X, Wu Z, Gao H, Cai X, Ruan G, *et al*: High-throughput proteomic analysis of FFPE tissue samples facilitates tumor stratification. Mol Oncol 13: 2305-2328, 2019.
56. Kurtin PJ: Mantle cell lymphoma. Adv Anat Pathol 5: 376-398, 1998.
57. Palomero J, Vegliante MC, Rodríguez ML, Eguileor A, Castellano G, Planas-Rigol E, Jares P, Ribera-Cortada I, Cid MC, Campo E, *et al*: SOX11 promotes tumor angiogenesis through transcriptional regulation of PDGFA in mantle cell lymphoma. Blood 124: 2235-2247, 2014.
58. Hanel W, Lata P, Youssef Y, Tran H, Tsyba L, Sehgal L, Blaser BW, Huszar D, Helmig-Mason J, Zhang L, *et al*: A sumoylation program is essential for maintaining the mitotic fidelity in proliferating mantle cell lymphoma cells. Exp Hematol Oncol 11: 40, 2022.
59. Lokhande L, Nilsson D, de Matos Rodrigues J, Hassan M, Olsson LM, Pyl PT, Vasquez L, Porwit A, Gerdtsson AS, Jerkeman M, *et al*: Quantification and profiling of early and late differentiation Stage T cells in mantle cell lymphoma reveals immunotherapeutic targets in subsets of patients. Cancers (Basel) 16: 2289, 2024.
60. Zhou Y, Heesom K, Osborn K, AlMohammed R, Sweet SM and Sinclair AJ: Identifying the cellular interactome of Epstein-barr virus lytic regulator zta reveals cellular targets contributing to viral replication. J Virol 94: e00927-19, 2020.
61. Xu H, Perez RD, Frey TR, Burton EM, Mannemuddhu S, Haley JD, McIntosh MT and Bhaduri-McIntosh S: Novel replisome-associated proteins at cellular replication forks in EBV-transformed B lymphocytes. PLoS Pathog 15: e1008228, 2019.
62. El-Mallawany NK, Day N, Ayello J, Van de Ven C, Conlon K, Fermin D, Basrur V, Elenitoba-Johnson K, Lim M and Cairo MS: Differential proteomic analysis of endemic and sporadic Epstein-Barr virus-positive and negative Burkitt lymphoma. Eur J Cancer 51: 92-100, 2015.
63. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2018. CA Cancer J Clin 68: 7-30, 2018.
64. Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP, Gregor M, Cymbalista F, Buske C, Hillmen P, *et al*: Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 32: 23-33, 2021.
65. Ikhlef L, Ratti N, Durand S, Formento R, Daverat H, Boutaud M, Guillou C, Dmytruk N, Gachard N, Cosette P, *et al*: Extracellular vesicles from type-2 macrophages increase the survival of chronic lymphocytic leukemia cells ex vivo. Cancer Gene Ther 31: 1164-1176, 2024.
66. Aslan B, Manyam G, Iles LR, Tantawy SI, Desikan SP, Wierda WG and Gandhi V: Transcriptomic and proteomic differences in BTK-WT and BTK-mutated CLL and their changes during therapy with pirtobrutinib. Blood Adv 8: 4487-4501, 2024.
67. Griffen TL, Hoff FW, Qiu Y, Lillard JW Jr, Ferrajoli A, Thompson P, Toro E, Ruiz K, Burger J, Wierda W, *et al*: Proteomic profiling based classification of CLL provides prognostication for modern therapy and identifies novel therapeutic targets. Blood Cancer J 12: 43, 2022.
68. Liu Z, Liu J, Zhang T, Shi M, Chen X, Chen Y and Yu J: Destabilization of ROR1 enhances activity of Ibrutinib against chronic lymphocytic leukemia in vivo. Pharmacol Res 151: 104512, 2020.
69. Wang ML, Barrientos JC, Furman RR, Mei M, Barr PM, Choi MY, de Vos S, Kallam A, Patel K, Kipps TJ, *et al*: Zilovertamab vedotin targeting of ROR1 as therapy for lymphoid cancers. NEJM Evid 1: EVIDoa2100001, 2022.
70. Choi MY, Widhopf GF II, Ghia EM, Kidwell RL, Hasan MK, Yu J, Rassenti LZ, Chen L, Chen Y, Pittman E, *et al*: Phase I trial: Cirmtuzumab inhibits ROR1 signaling and stemness signatures in patients with chronic lymphocytic leukemia. Cell Stem Cell 22: 951-959.e3, 2018.
71. Johnston HE, Carter MJ, Larrayoz M, Clarke J, Garbis SD, Oscier D, Strefford JC, Steele AJ, Walewska R and Cragg MS: Proteomics profiling of CLL Versus Healthy B-cells identifies putative therapeutic targets and a Subtype-independent signature of spliceosome dysregulation. Mol Cell Proteomics 17: 776-791, 2018.
72. Bagacean C, Iuga CA, Bordron A, Tempescul A, Pralea IE, Bernard D, Cornen M, Bergot T, Le Dantec C, Brooks W, *et al*: Identification of altered cell signaling pathways using proteomic profiling in stable and progressive chronic lymphocytic leukemia. J Leukoc Biol 111: 313-325, 2022.
73. Wu Y, Jin M, Fernandez M, Hart KL, Liao A, Ge X, Fernandes SM, McDonald T, Chen Z, Röth D, *et al*: METTL3-Mediated m6A modification controls splicing factor abundance and contributes to aggressive CLL. Blood Cancer Discov 4: 228-245, 2023.
74. Subramaniam N, Bottek J, Thiebes S, Zec K, Kudla M, Soun C, de Dios Panal E, Lill JK, Pfennig A, Herrmann R, *et al*: Proteomic and bioinformatic profiling of neutrophils in CLL reveals functional defects that predispose to bacterial infections. Blood Adv 5: 1259-1272, 2021.
75. Ecker V, Brandmeier L, Stumpf M, Giansanti P, Moreira AV, Pfeuffer L, Fens M, Lu J, Kuster B, Engleitner T, *et al*: Negative feedback regulation of MAPK signaling is an important driver of chronic lymphocytic leukemia progression. Cell Rep 42: 113017, 2023.
76. Beckmann L, Berg V, Dickhut C, Sun C, Merkel O, Bloehdorn J, Robrecht S, Seifert M, da Palma Guerreiro A, Claasen J, *et al*: MARCKS affects cell motility and response to BTK inhibitors in CLL. Blood 138: 544-556, 2021.
77. Stachelscheid J, Jiang Q, Aszyk C, Warner K, Bley N, Müller T, Vydzhak O, Symeonidis K, Crispatzu G, Mayer P, *et al*: The proto-oncogene TCL1A deregulates cell cycle and genomic stability in CLL. Blood 141: 1425-1441, 2023.
78. Griffen TL, Hoff FW, Qiu Y, Burger J, Wierda W and Kornblau SM: Prognostication of DNA damage response protein expression patterns in chronic lymphocytic leukemia. Int J Mol Sci 24: 1425-1441, 2023.
79. Saberi Hosnijeh F, van der Straten L, Kater AP, van Oers MHJ, Posthuma WFM, Chamuleau MED, Bellido M, Doorduijn JK, van Gelder M, Hoogendoorn M, *et al*: Proteomic markers with prognostic impact on outcome of chronic lymphocytic leukemia patients under chemo-immunotherapy: Results from the HOVON 109 study. Exp Hematol 89: 55-60.e6, 2020.
80. Lu J, Cannizzaro E, Meier-Abt F, Scheinost S, Bruch PM, Giles HA, Lütge A, Hüllein J, Wagner L, Giacopelli B, *et al*: Multi-omics reveals clinically relevant proliferative drive associated with mTOR-MYC-OXPHOS activity in chronic lymphocytic leukemia. Nat Cancer 2: 853-864, 2021.

81. van Dijk AD, Griffen TL, Qiu YH, Hoff FW, Toro E, Ruiz K, Ruvolo PP, Lillard JW Jr, de Bont E, Burger JA, *et al*: RPPA-based proteomics recognizes distinct epigenetic signatures in chronic lymphocytic leukemia with clinical consequences. Leukemia 36: 712-722, 2022.
82. Hengeveld PJ, Kolijn PM, Demmers JAA, Doff W, Dubois JMN, Rijken M, Assmann J, van der Straten L, Boiten HJ, Gussinklo KJ, *et al*: High-throughput proteomics identifies THEMIS2 as independent biomarker of Treatment-free survival in untreated CLL. Hemasphere 7: e951, 2023.
83. Jacobsen E: Follicular lymphoma: 2023 update on diagnosis and management. Am J Hematol 97: 1638-1651, 2022.
84. Sorigue M and Sancho JM: Recent landmark studies in follicular lymphoma. Blood Rev 35: 68-80, 2019.
85. Enemark MBH, Wolter K, Campbell AJ, Andersen MD, Sørensen EF, Hybel TE, Madsen C, Lauridsen KL, Plesner TL, Hamilton-Dutoit SJ, *et al*: Proteomics identifies apoptotic markers as predictors of histological transformation in patients with follicular lymphoma. Blood Adv 7: 7418-7432, 2023.
86. Monrad I, Madsen C, Lauridsen KL, Honoré B, Plesner TL, Hamilton-Dutoit S, d'Amore F and Ludvigsen M: Glycolytic biomarkers predict transformation in patients with follicular lymphoma. PLoS One 15: e0233449, 2020.
87. Ludvigsen M, Madsen C, Kamper P, Hamilton-Dutoit SJ, Bendix K, d'Amore F and Honoré B: Histologically transformed follicular lymphoma exhibits protein profiles different from both Non-transformed follicular and de novo diffuse large B-cell lymphoma. Blood Cancer J 5: e293, 2015.
88. Deng Y, Ma J, Zhao S, Yang M, Sun Y and Zhang Q: Expression of glucose transporter-1 in follicular lymphoma affected tumor-infiltrating immunocytes and was related to progression of disease within 24 months. Transl Oncol 28: 101614, 2023.
89. Radtke AJ, Postovalova E, Varlamova A, Bagaev A, Sorokina M, Kudryashova O, Meerson M, Polyakova M, Galkin I, Svekolkin V, *et al*: Multi-omic profiling of follicular lymphoma reveals changes in tissue architecture and enhanced stromal remodeling in high-risk patients. Cancer Cell 42: 444-463.e10, 2024.
90. Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, *et al*: Obinutuzumab for the First-line treatment of follicular lymphoma. N Engl J Med 377: 1331-1344, 2017.
91. Duś-Szachniewicz K, Rymkiewicz G, Agrawal AK, Kołodziej P and Wiśniewski JR: Large-scale proteomic analysis of follicular lymphoma reveals extensive remodeling of cell adhesion pathway and identifies hub proteins related to the lymphomagenesis. Cancers (Basel) 13: 630, 2021.
92. Cheah CY and Seymour JF: Marginal zone lymphoma: 2023 update on diagnosis and management. Am J Hematol 98: 1645-1657, 2023.
93. Di Rocco A, Petrucci L, Assanto GM, Martelli M and Pulsoni A: Extranodal Marginal zone lymphoma: Pathogenesis, diagnosis and treatment. Cancers (Basel) 14: 1742, 2022.
94. Zucca E and Bertoni F: The spectrum of MALT lymphoma at different sites: Biological and therapeutic relevance. Blood 127: 2082-2092, 2016.
95. Shi J, Zhou M, Zhou X, Jia S, Liu Z, Zhao Y, Shi J, Song X, Wang Y, Jia R, *et al*: Multi-omics and case-control analyses identify immunoglobulin M as a Tumour-derived serum biomarker of ocular adnexal extranodal marginal zone lymphoma. Clin Transl Med 13: e1259, 2023.
96. Shi J, Zhu T, Lin H, Liu Z, Zhou M, Yu Z, Zhou X, Song X, Wang Y, Jia R, *et al*: Proteotranscriptomics of ocular adnexal B-cell lymphoma reveals an oncogenic role of alternative splicing and identifies a diagnostic marker. J Exp Clin Cancer Res 41: 234, 2022.
97. Zhu T, Shi J, Zhou X, Qiu C, Jia R, Huang S, Jia R, Wang Y, Song X and Zhou Y: MYC-targeted genes predict distant recurrence in patients with ocular adnexal extranodal marginal zone lymphoma. Ann Hematol 102: 2413-2423, 2023.
98. Zucca E, Bertoni F, Stathis A and Cavalli F: Marginal zone lymphomas. Hematol Oncol Clin North Am 22: 883-901, 2008.
99. Thandra KC, Barsouk A, Saginala K, Padala SA, Barsouk A and Rawla P: Epidemiology of Non-Hodgkin's Lymphoma. Med Sci (Basel) 9: 5, 2021.
100. Mariette X and Criswell LA: Primary Sjögren's Syndrome. N Engl J Med 378: 931-939, 2018.
101. Jazzar AA, Shirlaw PJ, Carpenter GH, Challacombe SJ and Proctor GB: Salivary S100A8/A9 in Sjögren's syndrome accompanied by lymphoma. J Oral Pathol Med 47: 900-906, 2018.
102. Cui L, Elzakra N, Xu S, Xiao GG, Yang Y and Hu S: Investigation of three potential autoantibodies in Sjogren's syndrome and associated MALT lymphoma. Oncotarget 8: 30039-30049, 2017.
103. Zou Q, Zhang H, Meng F, He L, Zhang J and Xiao D: Proteomic and transcriptomic studies of BGC823 cells stimulated with Helicobacter pylori isolates from gastric MALT lymphoma. PLoS One 15: e0238379, 2020.
104. Tang X, Yang ZZ, Kim HJ, Anagnostou T, Yu Y, Wu X, Chen J, Krull JE, Wenzl K, Mondello P, *et al*: Phenotype, function, and clinical significance of CD26+ and CD161+tregs in splenic marginal zone lymphoma. Clin Cancer Res 28: 4322-4335, 2022.
105. Liu X, Yang M, Wu M, Zheng W, Xie Y, Zhu J, Song Y and Liu W: A retrospective study of the CHOP, CHOPE, and CHOPE/G regimens as the first-line treatment of peripheral T-cell lymphomas. Cancer Chemother Pharmacol 83: 443-449, 2019.
106. Ludvigsen M, Bjerregård Pedersen M, Lystlund Lauridsen K, Svenstrup Poulsen T, Hamilton-Dutoit SJ, Besenbacher S, Bendix K, Møller MB, Nørgaard P, d'Amore F and Honoré B: Proteomic profiling identifies outcome-predictive markers in patients with peripheral T-cell lymphoma, not otherwise specified. Blood Adv 2: 2533-2542, 2018.
107. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 89: 3909-3918, 1997.
108. Mora J, Filippa DA, Thaler HT, Polyak T, Cranor ML and Wollner N: Large cell non-Hodgkin lymphoma of childhood: Analysis of 78 consecutive patients enrolled in 2 consecutive protocols at the memorial Sloan-kettering cancer center. Cancer 88: 186-197, 2000.
109. Ferreri AJ, Govi S, Pileri SA and Savage KJ: Anaplastic large cell lymphoma, ALK-positive. Crit Rev Oncol Hematol 83: 293-302, 2012.
110. Rajan SS, Amin AD, Li L, Rolland DC, Li H, Kwon D, Kweh MF, Arumov A, Roberts ER, Yan A, *et al:* The mechanism of cancer drug addiction in ALK-positive T-Cell lymphoma. Oncogene 39: 2103-2117, 2020.
111. Lovisa F, Garbin A, Crotti S, Di Battista P, Gallingani I, Damanti CC, Tosato A, Carraro E, Pillon M, Mafakheri E, *et al*: Increased Tenascin C, Osteopontin and HSP90 levels in plasmatic small extracellular vesicles of pediatric ALK-positive anaplastic large cell lymphoma: New prognostic biomarkers? Diagnostics (Basel) 11: 253, 2021.
112. Hu M, Bao R, Lin M, Han XR, Ai YJ, Gao Y, Guan KL, Xiong Y and Yuan HX: ALK fusion promotes metabolic reprogramming of cancer cells by transcriptionally upregulating PFKFB3. Oncogene 41: 4547-4559, 2022.
113. Wei C, Li W, Qin L, Liu S, Xue C, Ren K, Zhang Z, Liu C, Bao F, Zhang H, *et al*: Clinicopathologic characteristics, outcomes, and prognostic factors of angioimmunoblastic T-cell lymphoma in China. Cancer Med 12: 3987-3998, 2023.
114. Holst JM, Enemark MB, Pedersen MB, Lauridsen KL, Hybel TE, Clausen MR, Frederiksen H, Møller MB, Nørgaard P, Plesner TL, *et al*: Proteomic Profiling differentiates lymphoma patients with and without concurrent myeloproliferative neoplasia. Cancers (Basel) 13: 5526, 2021.
115. Au WY, Weisenburger DD, Intragumtornchai T, Nakamura S, Kim WS, Sng I, Vose J, Armitage JO and Liang R: Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: A study of 136 cases from the international peripheral T-Cell lymphoma project. Blood 113: 3931-3937, 2009.
116. Wang H, Fu BB, Gale RP and Liang Y: NK-/T-cell lymphomas. Leukemia 35: 2460-2468, 2021.
117. Xiong J, Cui BW, Wang N, Dai YT, Zhang H, Wang CF, Zhong HJ, Cheng S, Ou-Yang BS, Hu Y, *et al*: Genomic and transcriptomic characterization of natural Killer T cell lymphoma. Cancer Cell 37: 403-419.e6, 2020.
118. Li Q, Zeng H, Zhao Y, Gong Y and Ma X: Proteomic analysis of cerebrospinal fluid from patients with extranodal NK-/T-Cell lymphoma of Nasal-type with ethmoidal sinus metastasis. Front Oncol 9: 1489, 2019.
119. Lim SH, Hong JY, Lim ST, Hong H, Arnoud J, Zhao W, Yoon DH, Tang T, Cho J, Park S, *et al*: Beyond first-line non-anthracycline-based chemotherapy for extranodal NK/T-cell lymphoma: Clinical outcome and current perspectives on salvage therapy for patients after first relapse and progression of disease. Ann Oncol 28: 2199-2205, 2017.
120. Zhou Z, Li Z, Sun Z, Zhang X, Lu L, Wang Y and Zhang M: S100A9 and ORM1 serve as predictors of therapeutic response and prognostic factors in advanced extranodal NK/T cell lymphoma patients treated with pegaspargase/gemcitabine. Sci Rep 6: 23695, 2016.

121. Gong Y, Pu W, Jin H, Yang P, Zeng H, Wang Y, Pang F and Ma X: Quantitative proteomics of CSF reveals potential predicted biomarkers for extranodal NK-/T-cell lymphoma of nasal-type with ethmoidal sinus metastasis. Life Sci 198: 94-98, 2018.
122. Qiu Y, Zhou Z, Li Z, Lu L, Li L, Li X, Wang X and Zhang M: Pretreatment 14-3-3 epsilon level is predictive for advanced extranodal NK/T cell lymphoma therapeutic response to asparaginase-based chemotherapy. Proteomics Clin Appl: Oct 24, 2016 (Epub ahead of print). doi: 10.1002/prca.201600111.
123. Bobrowicz M, Fassnacht C, Ignatova D, Chang YT, Dimitriou F and Guenova E: Pathogenesis and therapy of primary cutaneous T-Cell lymphoma: Collegium internationale allergologicum (CIA) update 2020. Int Arch Allergy Immunol 181: 733-745, 2020.
124. Sethi TK, Montanari F, Foss F and Reddy N: How we treat advanced stage cutaneous T-cell lymphoma-mycosis fungoides and Sézary syndrome. Br J Haematol 195: 352-364, 2021.
125. Techner JM, Hooper MJ, Evans S, LeWitt TM, Paller AS, Guitart J, Lu KQ and Zhou XA: Skin tape strip proteomics in mycosis fungoides identifies Tumor-associated biomarkers. J Invest Dermatol 143: 517-520.e12, 2023.
126. Qureshi HA, Azimi A, Wells J and Fernandez-Penas P: Tape stripped stratum corneum samples are suitable for diagnosis and comprehensive proteomic investigation in mycosis fungoides. Proteomics Clin Appl 17: e2200039, 2023.
127. Leng L, Liu Z, Ma J, Zhang S, Wang Y, Lv L, Zhu Y, Gao D, Wang Y, Wang J, *et al*: Proteomic identification of new diagnostic biomarkers of early-stage cutaneous mycosis fungoides. Cancer Commun (Lond) 42: 558-562, 2022.
128. Lemchak D, Banerjee S, Digambar SS, Hood BL, Conrads TP, Jedrych J, Geskin L and Akilov OE: Therapeutic and prognostic significance of PARP-1 in advanced mycosis fungoides and Sezary syndrome. Exp Dermatol 27: 188-190, 2018.