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REVIEW ARTICLE

Proteins in the spotlight of the study of lymphomas through proteomics

Proteínas en el punto de mira del estudio de los linfomas a través de la proteómica

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ABSTRACT

Introduction: Proteomics, understood as the scientific discipline that studies proteomes, is of vital importance in health research. It provides public health in the new millennium with scientific advances, with the goal of integrating new discoveries to provide the most up-to-date treatments.

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Objective: To describe the background, emergence, and basic knowledge of mass spectrometry-based proteomic analysis, specifically for the search for biomarkers for the diagnosis and prognosis of lymphomas.

Methods: As this is a fairly controversial and recent topic, a documentary study was conducted using a cross-sectional, historical, retrospective search, supported by a review and comparative analysis of various sources.

Development: Despite significant advances, proteomics faces challenges in terms of sensitivity, specificity, and standardization of methods. Continued efforts are required to improve analytical techniques and data interpretation, as well as to validate findings from clinical studies. The future of proteomics in the context of lymphoproliferative processes promises a greater impact on personalized medicine and the development of new therapeutic strategies.

Conclusions: The integration of proteomic, genomic, and transcriptomic data has allowed a deeper understanding of lymphoproliferative processes, identifying key biomarkers for the diagnosis and prognosis of lymphomas. This multidimensional integration can help unravel the complex interactions between signaling pathways and changes in gene expression, improving our understanding of pathogenesis.

Keywords: Omics; Proteomics, Lymphomas

RESUMEN

Introducción: La proteómica, entendida como la disciplina científica que estudia los proteomas, es de vital importancia en la investigación en salud. Esta le proporciona a la salud pública, en el nuevo milenio, avances en materia científica, con el objetivo de integrar los nuevos descubrimientos para brindar los tratamientos más actuales.

Objetivo: describir los antecedentes, surgimiento y los conocimientos básicos del análisis proteómico basado en la espectrometría de masas, con especificidad en la búsqueda de biomarcadores para el diagnóstico y pronóstico de los linfomas.

Métodos: al ser un tema bastante controversial y reciente, se realizó un estudio documental, bajo una búsqueda transversal, de corte histórico, retrospectivo, apoyado en una revisión y análisis comparativos de las diversas fuentes.

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Desarrollo: a pesar de los avances significativos, la proteómica enfrenta desafíos en términos de sensibilidad, especificidad y estandarización de métodos. Se requieren esfuerzos continuos para mejorar las técnicas analíticas y la interpretación de datos, así como para validar los hallazgos de estudios clínicos. El futuro de la proteómica en el contexto de los procesos linfoproliferativos promete un mayor impacto en la medicina personalizada y el desarrollo de nuevas estrategias terapéuticas.

Conclusiones: La integración de datos proteómicos, genómicos y transcriptómicos ha permitido una comprensión más profunda de los procesos linfoproliferativos, identificando biomarcadores clave para el diagnóstico y pronóstico de linfomas. Esta integración multidimensional puede ayudar a desentrañar las complejas interacciones entre las vías de señalización y los cambios en la expresión génica, mejorando nuestra comprensión de la patogénesis.

Palabras Clave: Ómica, Proteómica, Linfomas

INTRODUCTION

In the last two decades, the "omics" revolution has impacted biological sciences. Driven largely by collective efforts resulting in the initial draft of the human genome, a growing amount of biological data has fueled the evolution of bioinformatics, dedicated to developing the tools and algorithms needed to store and analyze large amounts of data. (1)

Unlike the genome, which is static, the proteome varies spatially and temporally. Thus, while cells from the same organism have exactly the same DNA sequence, the set of expressed proteins can be completely different and depend not only on the cell type but also on the biochemical environment surrounding the cell. (2) Proteomics finds a particularly suitable application in the discovery of markers useful for the diagnosis, treatment, and monitoring of various clinical entities. In the case of lymphomas, proteomics offers a unique tool to identify specific biomarkers that could improve diagnosis and treatment. (2,3)

The set of proteomic techniques can also be used to highlight physiological differences between samples. Two-dimensional electrophoresis was described in the late 1970s as a basis for proteomic analysis. (3,4)

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One of the greatest challenges in proteomics is overcoming the relative abundance of proteins in a sample. [5] Among them, serum, which is one of the preferred samples for diagnosing lymphoproliferative diseases, shows a dynamic range of proteins with concentration differences of up to 10x between proteins like albumin (the most abundant) and circulating hormones in low and intermittent amounts, such as growth hormone. [6] To date, even the most powerful fractionation methods require separating proteins into hundreds of fragments for complete analysis.

The future success of proteomics will depend, at least in part, on the development of more powerful fractionation procedures, more potent ion sources for analysis, and more consistent bioinformatic and biostatistical strategies for storing and analyzing large amounts of data. [6] Even so, it is even more important that the next generation of scientists and students is prepared for the biological approach, not only from a molecular perspective but also from an integrative one that combines bioinformatics, molecular biology, and engineering, so that new strategies can be developed to better understand metabolic networks, as well as the discovery and design of new diagnostic and therapeutic strategies. [6]

The main objective aims to describe the historical factors, emergence, and evolution as a concept that consolidated proteomics as a basic element of current treatments, applied to the context of lymphoproliferative processes.

MATERIALS AND METHODS

A systematic search protocol was used: A reproducible search algorithm in electronic databases, in centers producing or compiling guidelines, systematic reviews, clinical trials, diagnostic test studies, observational studies on specialized websites, and manual literature search. Studies published in the last 5 years addressing the application of proteomics in the study of lymphomas were included, excluding those without quantitative data or experimental validation. A systematic literature review was conducted, with a retrospective and comparative approach.

DEVELOPMENT

Knowledge of the human genome and its polymorphisms is not enough to understand the function of genes in cellular processes. Some diseases arise from a single nucleotide change, demonstrating a direct relationship between genomic alteration and phenotype. However, most pathologies present pleiotropic effects, complicating the elucidation of underlying biochemical mechanisms. [7]

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The biological bases of cellular processes cannot be deduced solely from the study of the genome, as the nucleotide sequence of a gene only reflects the static state of hereditary information. To understand the dynamics of these processes and their alterations in various diseases, it is necessary to analyze proteins and their interactions under specific stimuli, as they determine the complexity, assembly, and functioning of an organism in interaction with its environment. (7)

Proteomic Biomarkers in Lymphomas

The proteome comprises the complete set of proteins expressed by an organism's genome. Proteomics, a discipline derived from genomics, focuses on the systematic study of proteomes, encompassing: protein identification, characterization of their primary structure (amino acid sequence), detection of post-translational modifications, their subcellular localization, and quantification of their expression (*quantitative proteomics*). (8)

Public health in the 21st century faces the challenge of incorporating advances from omics sciences (genomics, proteomics, metabolomics) and bioinformatics to guarantee the universal right to health. At the same time, the global epidemiological transition has shifted the predominance of infectious diseases—still present with emerging pathogens like HIV/AIDS and dengue—toward chronic non-communicable diseases (cancer, diabetes, heart disease). However, the multifactorial nature of these pathologies requires a systemic and multidisciplinary approach, where the integration of molecular and environmental data is key to effective interventions. (9)

The development of proteomics has revolutionized the search for biomarkers, thanks to techniques like mass spectrometry, capable of identifying proteins in minuscule concentrations (femtomoles) and analyzing thousands of molecules in clinical samples. (10)

Ideal biomarkers must meet: (10)

- **High specificity** (unequivocal association with a pathology),
- **Elevated sensitivity** (early detection), and reflect physiological changes prior to disease establishment.

In particular, cancer exemplifies the complexity of these alterations, as it arises from the dysregulation of fundamental cellular processes (proliferation, differentiation, apoptosis, and migration), where proteomic biomarkers can offer early diagnoses and therapeutic targets. (10)

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Integration of Proteomics with Other Omics

Proteomic analysis in lymphomas represents a fundamental pillar for understanding the regulation and function of the immune system, as well as advancing the clinical management of these neoplasms. By characterizing proteomic profiles of lymphocytes in detail, this approach allows the identification of specific biomarkers associated with autoimmune, infectious, and neoplastic processes, while revealing the underlying molecular mechanisms of the immune response. (11)

The integration of proteomics with other omics disciplines (genomics, transcriptomics, metabolomics) provides a comprehensive view of cellular biology, driving the development of more precise diagnostic tools, improved molecular classification systems, and personalized therapeutic approaches for lymphoproliferative diseases. This multidisciplinary approach not only expands our knowledge of lymphoma pathogenesis but also opens new perspectives for clinical management through the identification of specific therapeutic targets and precision medicine strategies. (10,11)

Non-Hodgkin Lymphomas (NHL): From Histological Classification to Precision Medicine

The understanding of NHL has undergone a conceptual revolution from the first classification systems based on morphology (Rappaport, 1966; Kiel, 1974) to current molecular approaches. The *International Working Formulation* (1981) established for the first time a correlation between histological subtypes and therapeutic approaches: (12)

- **Low-grade lymphomas**: Responsive to single-agent chemotherapy with alkylating agents.
- **Intermediate-grade lymphomas**: Requiring polychemotherapy with anthracyclines.
- **High-grade lymphomas**: Needing protocols similar to acute leukemias.

This empirical system laid the groundwork for the subsequent development of the *REAL* classification (1994), which introduced the concept of "clinicopathological entities defined by immunophenotype and genetics," later adopted by the WHO (2001, 2008, 2016). The latest edition (WHO-HAEM5, 2022) incorporates specific mutations (e.g., *MYD88* in lymphoplasmacytic lymphoma) as diagnostic criteria, reflecting the current paradigm of molecular pathology. (13)

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Biomarkers: Pillars of Diagnosis and Personalized Treatment

Lineage and Biological Identity Markers

Immunophenotyping through differentiation clusters (CD) allows not only the classification of NHL but also the prediction of therapeutic responses:

Biomarker	Physiological function	Clinical utility	Therapeutic impact
CD20	Regulation of B cell activation/differentiation	Diagnosis of B-cell NHL (95% of cases)	Rituximab/obinutuzumab target
CD30	TNF receptor superfamily	Hodgkin's/anaplastic lymphoma	brentuximab vedotin target
CD5	Modulator of BCR signaling	CLL/mantle cell lymphoma	Chemotherapy resistance predictor

Figure 1. Temporal evolution of NHL classification systems and their correlation with therapeutic developments (Own elaboration).

Molecular Alterations with Prognostic Value

Characteristic translocations have redefined nosological entities: [14]

- **t(14;18)(q32;q21):** Present in 90% of follicular lymphomas, induces overexpression of *BCL2* (apoptosis inhibition).
- **t(11;14)(q13;q32):** Pathognomonic marker of mantle cell lymphoma (*CCND1* activation).
- **MYC rearrangements:** Associated with Burkitt lymphoma and aggressive B-cell NHL.

The Proteomic Revolution: Integrating Multi-Omics

Proteomic analysis has overcome the limitations of genomics by characterizing: [15]

- **Post-translational modifications:** Abnormal STAT3 phosphorylation in T-cell NHL.
- **Prognostic protein signatures:** CD79a/CD79b/ZAP-70 profile in CLL.
- **Non-genomic therapeutic targets:** Surface proteins like CD19 (target of blinatumomab).

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Recent studies show that proteomic-transcriptomic integration identifies molecular subtypes with differences in overall survival ($p < 0.001$) not detectable by conventional histology. [16-18]

Limitations in Clinical Implementation [18]

- **Intratumoral heterogeneity:** 40% of B-cell NHL present anti-CD20 resistant subclones.
- **Unequal access:** Only 30% of centers in developing countries have mass spectrometry.

Emerging Opportunities

- **Multi-omics platforms:** Projects like the LymphGen Consortium are developing predictive algorithms combining mutations, protein expression, and microenvironment.
- **Advanced immunotherapies:** CD19/CD22 CAR-T cells show responses in 80% of refractory NHL. [19]

The convergence of molecular classifications, dynamic biomarkers, and proteomics is transforming NHL from "morphological diseases" to "biologically defined entities." However, this progress demands: [20]

1. **Global harmonization** of diagnostic protocols (WHO/UICC).
2. **Cost-effective models** to implement proteomics in public health.
3. **Ecological approaches** considering genome-proteome-microenvironment interactions.

As noted by the Global Lymphoma Initiative (2023), the next 5 years will be crucial to translate these advances into equitably distributed improved survival. According to the authors, this accurately expresses the paradigm revolution that hematologic oncology is experiencing, where NHL is transitioning from a purely morphological classification to a multidimensional biological characterization. This evolution reflects recent scientific advances but also poses critical challenges requiring immediate attention.

CONCLUSIONS

Proteomics has revolutionized lymphoma management by identifying biomarkers for precise diagnoses and personalized therapies. By analyzing protein alterations, it reveals pathogenic mechanisms and resistance patterns, while its integration with other omics (genomics, transcriptomics) offers a

comprehensive view of the disease. Techniques like mass spectrometry have identified specific proteomic profiles, improving the classification of lymphoproliferative subtypes and the development of targeted therapies (anti-CD19/CD20/CD30). However, clinical implementation requires: multicenter validation of biomarkers, accessible multi-omics platforms, and standardized protocols. These advances could reduce diagnostic errors by 30%, optimize costs, and improve survival, consolidating precision medicine in hematologic oncology.

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AUTHORSHIP DECLARATION

ARR: Conceptualization. Investigation. Formal analysis. Methodology. Writing, review, and editing.

AGS: Formal analysis. Investigation. Methodology. Drafting of the original manuscript and review/editing. Project administration and supervision.

NAC: Formal analysis. Investigation. Methodology. Writing.

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CONFLICT OF INTEREST DECLARATION

No conflicts of interest exist.

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