Chapter 5 The omics era: proteomics importance in cancer research

Capítulo 5 La era ómica: importancia de la proteómica en la investigación del cáncer

VALLEJO-CARDONA, Alba Adriana†*, ROJAS-CERVANTES, Karen Olivia, VERDUGO-MOLINARES, Maritza Guadalupe and LIMÓN-ROJAS, Areli

Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco A.C (CIATEJ-CONACYT). Área de Biotecnología Médica y Farmacéutica. México.

ID 1st Author: *Alba Adriana, Vallejo-Cardona* / **ORC ID:** 0000-0002-45683787, **Researcher ID Thomson:** G-8039-2019, **CVU CONACYT ID:** 50109

ID 1st Co-author: *Karen Olivia, Rojas-Cervantes* / **ORC ID:** 0000-0002-6615-6310, **CVU CONACYT ID:** 1136621

ID 2nd Co-author: *Maritza Guadalupe, Verdugo-Molinares* / **ORC ID:** 0000-0002-8413-0229, **CVU CONACYT ID:** 1124919

ID 3rd Co-author: *Areli, Limón-Rojas* / **ORC ID:** 0000-0002-0280-0170, **CVU CONACYT ID:** 1023352

DOI: 10.35429/H.2022.5.1.44.55

* avallejo@ciatej.mx

A. Marroquín, M. Morales, J. Ramírez, L. Cruz. (Coord.) CIERMMI Women in Science TXVIII Health Sciences. Handbooks-

Abstract

Cancer is a pathology that leads the causes of death in the population worldwide also is reported its increase with enhancing of life expectancy. In addition, this pathology is multifactorial, including genetic mutations and environmental effectors such as germs or environmental compositional changes, considered as contaminating elements to the organism. For example, other direct factors are associated with chronic diseases that induced continue inflammation.

Therefore, understanding cancer biology and its mechanism of action is a fundamental part of mitigating its effect on public health. As a heterogeneous disease, his study is a constant challenge, identifying metastasis in the early stages and the resistance to drugs are problems with an unmet need that could be solved through the study of the disease at the molecular level.

Omics sciences have proven to be a promising option for the study of heterogeneous pathologies, due to their ability to analyze a biological system at the molecular level, quantify its composition, and group it according to its function. The study on which each science is based is by which it takes its name, genomics studies the genome, metabolomics the metabolome, proteomics the proteome, among others.

In this chapter, we will limit ourselves to proteomics, the study of the set of proteins of a biological system, which from our point of view is the omics science with the widest understanding and from which satisfactory results have been used in clinical application. Especially, because it has been possible to identify biomarkers that may be useful during the diagnosis or prognosis of the disease or therapeutic targets for personalized medicine in patients and thus minimize the adverse effects caused by drugs on healthy cells. We expose different proteomics studies applied in different biological systems such as cell lines, xenografts, and patient tissues or fluids, to reveal the versatility of the technique and the functionality of the data that have been obtained with it.

Proteomics, Pathology, Inflammation, Mechanisms, Biomarkers

Resumen

El cáncer es una patología que lidera las causas de muerte en la población a nivel mundial, y que ha aumentado con el incremento de la esperanza de vida. Además, se trata de una patología multifactorial, que incluye mutaciones genéticas y efectores ambientales como gérmenes o cambios en la composición ambiental que son considerados como contaminantes externos del organismo. Por ejemplo, otros factores directos están asociados con enfermedades crónicas que producen inflamación continua.

Por lo tanto, el entendimiento de la biología del cáncer y sus mecanismos de acción es una parte fundamental para mitigar su impacto en la salud pública. Al ser una enfermedad heterogénea, su estudio representa un constante reto, identificar la metástasis en etapas tempranas y la resistencia a medicamentos son problemas que no se han resuelto y podrían encontrar solución en el estudio de la enfermedad a nivel molecular. Las ciencias ómicas han demostrado ser una opción prometedora para el estudio de patologías heterogéneas, debido a su capacidad para analizar un sistema biológico a nivel molecular, cuantificar su composición y agruparlo según su función. El estudio al que se basa la ciencia le da su nombre, así, la genómica estudia el genoma, metabolómica se encarga del metaboloma, proteómica de las proteínas, entre otras.

En este capítulo nos limitaremos a la proteómica, el estudio del conjunto de proteínas de un sistema biológico, que desde nuestro punto de vista es la ciencia ómica mayormente estudiada y de la que se han obtenido resultados satisfactorios en su aplicación clínica, al permitir identificar biomarcadores que pueden ser utilizados durante el diagnóstico o pronóstico de la enfermedad al permitir encontrar dianas terapéuticas para la medicina personalizada en los pacientes y así minimizar los efectos adversos que provocan los fármacos sobre las células sanas. Exponemos diferentes estudios de proteómica aplicados en diferentes sistemas biológicos como líneas celulares, xenoinjertos y tejidos o fluidos de pacientes, para revelar la versatilidad de la técnica y la funcionalidad de los datos que se han obtenido con ella.

Proteómica, Patología, Inflamación, Mecanismos, Biomarcadores

5.1 Introduction

When we talk about cancer, we refer to conditions characterized by abnormal cellular behaviors outside of biological controls. All cancer (except for brain cancer and skin carcinoma that do not cause metastasis) has three characteristics: uncontrolled cell division, invasion, and destruction of normal tissues and colonization of distant sites being able to survive in an external environment of its origins and continuing its invasion (Compton, 2020).

A key step in the onset of cancer is the failure of cell death signaling pathways, which are activated by multiple causes of cell damage, such as DNA damage or mutation, activating caspase -9, -2, and -8 pathways or RIP kinases, the lack of control of these pathways will lead to the initiation of cancer (Gregory, 2016).

Knowing the origin of cancer is not the only option for the development of biomarkers and therapeutic targets is also important to study the tumor microenvironment as well as the mechanism involved in one of the most critical parts of cancer, the metastasis.

The tumor microenvironment includes Cancer-associated fibroblast (CAF), blood and lymphatic vessels, inflammatory cells, adipocytes, and neuroendocrine cells, all of them are present in the extracellular matrix (ECM) and made the structure of tissues and organs. Signaling proteins are involved too, such as cytokines and growth factors. All this interaction created signaling pathways that contribute to the progression and metastasis of cancer (Coban *et al*., 2021).

To cancer get to metastasis, it must follow a few steps, like a local invasion of the ECM and stromal cell layer, blood vessels, survival to the transportation around the vasculature, deposition in distant organs, extravasation, survival in a microenvironment different to his original one and finally the proliferation (Feng *et al*., 2020).

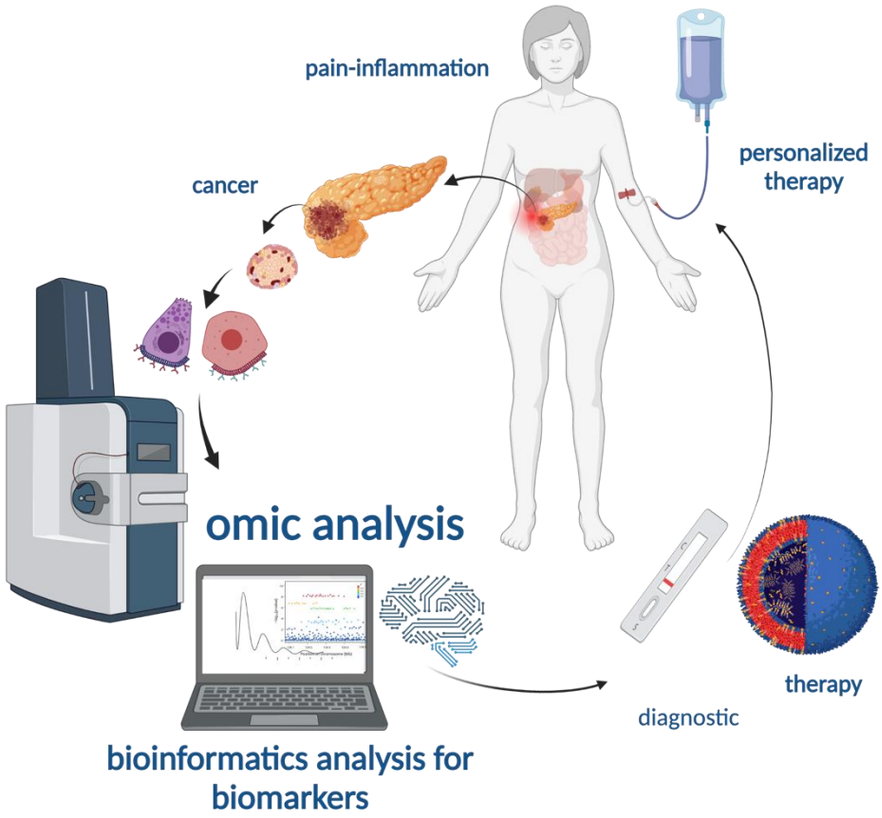
We can notice that cancer is a multifaceted disease. Over that 11 million people are diagnosed every year. The lack of early diagnosis is more related to cancer mortality than the availability of treatment. The advantages of early detection are detected cancer when is still localized and curable, which prevents mortality and reduces the comorbidities, this represents a lower cost to the health systems (Parisa Karimi *et al*., 2014).

One of the aims of actual medicine is the development of personalized medicine. In cancer, we know signaling pathways that are used as a therapeutic target. An example is the mutation of *EGFR* present in some cases of non-small cell lung cancer (NCSLC), this gen codified the epidermal growth factor receptor. If this mutation is identified, the patient is a candidate for treatment with erlotinib, a drug that blocks the action of the receptor and prevents the promotion of cell cancer proliferation (Mathé *et al*., 2018).

Even with the recent advance in treatments and diagnosis methods, most of them are invasives and inefficient in a lot of patients. It is still a challenge to expand and get better options for the patients, therefore, it is fundamental to continue with the search for new biomolecules or molecular changes that can work in the diagnosis, prognosis, or treatment of cancer.

New techniques and tools have revolutionized clinical medicine with the application of sciences such as genomics, proteomics, transcriptomics, metabolomics, and epigenomics that are integrated to form a new science field known as "omics". The development of these ‘omics’ technologies had a significant impact and created techniques of diagnosis faster, more sensitive, and more specific, as well as in the prognosis, treatment, and prevention of diseases, allowing the advent of new therapeutic strategies, with the identification of molecules that may be useful as new therapeutic targets and thus be able to offer personalized medicine to the patient (Figure 1.1) (Farfán & Torres, 2018; Ocana & Pandiella, 2010; Velásquez-Fernández D, 2011).

Figure 5.1 Use of multi-omic analysis for biomarker detection



5.2 Omics: understanding the biological systems

The investigation of omics science is referred to the use of technologies to analyze biological systems at a molecular level. These techniques are capable of reproducing data that are correlated with specific states of the biological systems. The molecules that the omics studied give it the name: metabolomics, proteomics, metabolomics, genomics, etc. (Rajesh *et al*., 2021).

The beginning of the omics era has significant big advances in biological sciences. Omics is the evolution from molecular biology to systems biology, changing the way to try to understand biological entities. The phenomenon of the interaction of biomolecules like DNA and proteins cannot be explained such as the determinate dogma central, it is imperative to study different levels of biomolecules and their interactions. If we get to integrate this information in the best way possible, we were able to reach the objective of omics in the clinic: recognize, evaluate, and applied biomarkers of diagnosis and prognosis (Colnaghi Simionato, 2021; Nguyen & Wangid, 2020).

The omics tools have permitted big progress in the identification of cancer markers like in Acute lymphoblastic leukemia (ALL). With genomics, it was possible to reveal acquired somatic disorders that can be used as markers such as translocation and aneuploidies, also it has been studied the role that plays the heritable genetic variations in the risk to have ALL. It has been important too, to understand the response to the drugs and the effects of the antineoplastic therapy. It is still necessary to continue with the identification of marks that can work to give information about the malignancy of pathologies such as ALL (Jiménez-Morales *et al*., 2017).

An important fact in the omics era is haven been the capacity to recollect useful information about biological systems, this issue is well explained in the review made by Kwon and collaborates (2021) where the recompilation of data is called multi-omics, which consists of the approach of the data generation of omics, creating a big-scale database given the possibility to make a big analysis of this information and use it to understand the biological systems. This can be focused on looking for data about a specific disease and its physiopathology and proteins, genes, metabolites, etc., and their interaction related to specific events.

We can mention a lot of sites of databases that integrated omics science such as The Cancer Genome Atlas (TCGA), The Human Protein Atlas, BAMS, BioGpS, GenBank, Catalogue of Somatic Mutations in Cancer (COSMIC), ENCODE project, UniProtKB, NIH cancer, UNIPROT, Proteomics DB, PRIDE, NCBI Structure Group, just to name a few ones.

The omics sciences have given us a lot of knowledge about cancer. Each one of them has provided valuable information to find out mechanisms of metastasis, resistance to drugs, metabolic pathways, etc. In all these omics science it is important to mention one that had given different biomarkers and therapeutics targets that are widely used in clinical practice, and it is necessary to personalized medicine, the proteomics.

The genome has all the hereditable information in the DNA, this biomolecule can transcript to RNA fragments, these fragments can or cannot codify proteins, and all the set of RNA is called transcriptome. The messenger RNA (mRNA) translates to proteins. Proteins are going to determine the functions of the cell and are necessary to cell life. But the quantity of proteins is not just related to the translation and its variation, also is involve post-translational modifications this generated a very large catalog of proteins. The set of proteins is called proteome. All these characteristics and variability are very important in the investigation of cell modification and tissue alteration. Proteomics not only revealed the complexity of life it is important to identify and study the alteration of the cell and its environment, during disease, treatment, or any specific situation. The proteome of a specific disease can give us clues about disease physiopathology (Ciocan-Cartita *et al*., 2019).

Knowing information about the genome is very important, as the exposed case of ALL and lung cancer, all these discoveries have made us question interesting things about cancer, but the conventional way of studying only one gene or one protein it is not enough to completely understand the disease, it is necessary to make a big-scale study. Genome study is very useful but another way to study the pathologies is using the genes products: the proteins (Lin *et al*., 2016).

If we think of cancer biomarkers that are used currently, we can mention CA 19-9, CA125, and CEA (carcinoembryonic antigen) all of them have common that are proteins (Mocan *et al*., 2022). Treatments like erlotinib or imatinib that can block the action of kinases to treat different types of cancer are a perfect example that the proteins are very important also like therapeutic targets (Asami, 2014; Buclin *et al*., 2020). It is easy to identify that studying these biomolecules is essential for clinical advances.

5.3 Proteomics and its usefulness in the study of cancer

Proteomics is the omic science in charge of studying the proteome of any biological system, this includes the structure of proteins, their functions, interactions, and modifications in any situation, using quantitative measurements to characterize any biological process and decipher its mechanisms.

The proteome of a living system provides fundamental details in the understanding of its biology, and how its biology is altered in the face of a certain specific physiological or pathological condition, the proteome tends to change in response to modifications of its normal conditions, providing fundamental information for the study of any pathology. Within diseases, the use of proteomics allows early diagnosis of diseases, prognosis, and monitoring of the disease, it is also necessary for the development of drugs as it allows the identification of therapeutic targets (Aslam *et al*., 2017).

Biochemical changes in the proteome of biological systems have provided important knowledge for the study of complex diseases, such as cancer, infectious diseases, neurodegenerative diseases, and diabetes, among others. Proteomic approaches locate and identify differential proteins at each stage of the disease for their correct treatment or eradication (Monti *et al*., 2019).

All cancers share a series of crucial capacities for the development of the tumor phenotype, such as proliferation even in the absence of growth factors, insensitivity to growth suppression mechanisms, angiogenesis, avoidance of apoptosis, tissue invasion, and metastasis. All the proteins involved in these characteristics will differ between the diseased and healthy individuals (Kruse *et al*., 2008).

Proteins are thought to drive tumor growth, tumor invasion, and response to targeted therapies, so identifying changes in protein signaling helps understand the mechanism of cancer progression. Cancer proteomics bases its studies on the quantification and analysis of proteins concerning their healthy counterparts, for the identification of information that helps the treatment of the disease (Shruthi *et al*., 2016; Srinivas *et al*., 2001)

In cancer, proteomics has become a fundamental omics science for the study of tumor growth and metastasis, contributing knowledge to the molecular biology of cancer. It allows us to explain the molecular mechanisms of malignant cells, as well as being able to analyze the tumor microenvironment (Hoi et al., 2017). As cancer progresses, the protein profiles present changes, which can be examined through quantitative proteomics, based on this it has been possible to identify biomarkers and locate protein expressions that could be used for tumor staging, prediction, or possible therapies (Kwon *et al*., 2021). Quantitative proteomics has been a good option for cell classification according to a pathological state, and in turn understanding its biological mechanism, also supporting the understanding of the mechanism of action and interaction of some drugs (Zhu *et al*., 2018). Since cancer could be considered a disease caused by abnormal transductions, aberrant signaling pathways are a promising therapeutic target (Pan *et al*., 2013). Proteomics is a very powerful tool to study signaling pathways and their possible alterations.

Proteins, being key molecules in biological processes, can be used as characteristic molecules of the different stages of cancer. The study of its structure, function, and quantification could improve patient outcomes. Some of the techniques for protein detection are ELISA, immunohistochemistry, fluorescence-activated cell sorting, and mass spectrometry, among others.

Pancreatic cancer is a type of cancer that is distinguished by its poor prognosis, which is why the identification of a biomarker in the early stage of cancer indicates an unmet need. Proteomic studies of pancreatic cancer have been carried out in patients (tissue, plasma, pancreatic juice, fluids), in cell cultures, or employing xenografts, where information has been sought on the mechanism of the disease. The proteomic approach appears promising in trying to identify a biomarker for early-stage disease however, it is an ongoing effort as this identification is challenging. Proteins that have been identified in the cell membrane have shown promise for biomarker development (Chen *et al*., 2005; Law *et al*., 2020; Le Large *et al*., 2019; Sanh N. *et al*., 2018).

5.4 The study of proteins

5.4.1 Cell line proteomics

Cancer cell lines are useful for the proteomic study of cancer in vivo, allowing a better understanding of cancer mechanisms and basic biology since for the most part, they retain the same characteristics as the tumor of origin. The use of cell lines presents easy manipulation and characterization, and high reproducibility, in addition to the fact that it is not necessary to obtain ethical permits for its use, however, any inadequate condition during its culture or the extraction of proteins will result in a loss in its morphology and turn to impair the proteomic characterization (D. Ferreira *et al*., 2013; van Staveren *et al*., 2009)

In a study of lung cancer, two cell lines characteristic of the disease, A549, and SW900, were analyzed by mass spectrometry, through which 68 proteins that were overexpressed in both cell lines could be identified. These proteins were classified into different functional processes. The comparison between the two proteomes allowed a more specific characterization of each cell line, A549 was related to cellular respiration, homeostasis, response to drugs, oxidative stress, and intracellular transport, while SW900 was related to the negative regulation of apoptosis, protein translation, and response to organic and inorganic substances (Korrodi-Gregório *et al*., 2016). Similarly, Katsogiannou *et al*. carried out a proteomic study using mass spectrometry of four cell lines belonging to prostate cancer, identified the over-expressed proteins in each cell line, and according to the identified proteins, functionally classified each cell line related to metabolism. transport and localization and identified some proteins related to resistance (Katsogiannou *et al*., 2019)

Cell lines are useful tools to investigate the molecular basis of cancer invasion. In a study by Pei et al., using a combination of electrophoresis and mass spectrometry, they analyzed the proteomes of cell lines U87MG and U343MG-A, which are lines cell characteristics of gliomas, the most lethal tumors of the brain, where it was possible to identify that annexin A2 was related to the invasion of the glioma, in the same way, Cathepsin D was seen as an important part in tumor progression, expressed more significantly in the U87MG cell line (Pei *et al*., 2014).

Chemoresistance is an obstacle during the treatment of diseases, so elucidation of the molecular mechanisms of resistance could lead to a response to therapy. In vitro analyzes of cell lines are a good option to elucidate these mechanisms. In an important study by Qinghong *et al*., they identified possible protein targets related to resistance to doxorubicin. The proteomes of cell lines belonging to leukemia were compared with control cells and the possible protective strategies to resist the drug were listed, concluding that it is a series of mechanisms that provides this resistance (Qinghong *et al*., 2015).

In another similar study by Albrethsen and colleagues, they compared the proteomics of six cell lines to test for resistance to agents that interact with microtubules and induce cell death. Galectin-1 was identified, as directly related to the resistance of the applied drugs, as well as stathmin, among other proteins (Albrethsen *et al*., 2014). Therefore, the proteomic analyzes applied to cell lines are not only functional for the characterization of the lines, but also for the application of various in vitro studies that support a better therapeutic response of the patient, as well as to explain the mechanisms and functions of the basic biology of cancer.

5.4.2 Proteomics in murine models

Cancer cells from cell line cultures or cells from cancer patients can be grafted into mouse models generating xenografts. D. Ferreira *et al*. (2013) mentioned that represents a greater similarity to the mechanisms of cancer in humans, however, the environment in which the tumor develops varies significantly, in addition to this it is necessary to have ethical permits for their manipulation.

Cancer-derived cachexia and muscle loss are associated with increased morbidity and mortality, so Hulmi and his team took on the task of developing an animal model of this condition, analyzing its proteome. With this analysis, they were able to study the alterations of the oxidative phosphorylation system and NAD+ homeostasis, with this information they proposed and tested an activin blocker that can restore depleted muscle NAD+ and Nrk2, being an example of the opportunities, it offers the study of the proteome and the applications of this knowledge (Hulmi *et al*., 2020).

R. Ferreira *et al*. (2019) used murine models of drug-induced urothelial carcinoma, a group that underwent exercise to study the change in the cardiac mitochondrial proteome that this activity caused, to study the cardiac effects observed in patients with cancer and the cardioprotective effect that exercise could have, and its mechanism. It was observed that from the outset, tumor induction by itself induces cardiac remodeling characterized by positive regulation of cardiac tissue morphogenesis and decreased cellular respiration, in mice that exercised it was shown that this was counteracted through the overexpression of cardiac muscle contraction proteins and ATP metabolism.

5.4.3 Proteomics in patients

The proteomic analysis of patients can be analyzed with a sample of the tissue of the tumor that has developed, but it is an invasive analysis for the patient and on some occasions, it is difficult to obtain, so biofluids such as blood, urine, saliva, tears, cerebrospinal fluid, prostatic secretions, among others, have also made it possible to identify clinically relevant proteins of the disease (Macklin *et al*., 2020).

Versatility in the use of samples is a crucial point. Currently, the characteristics and advantages of using these fluids to replace tissue biopsies have been analyzed and liquid biopsies have been determined. This option allows cover all aspects of cancer, unlike tissue biopsy, liquid biopsies could be useful for early detection, diagnosis, prognosis, and monitoring (Ding *et al*., 2021). The procedure consists of isolating entities derived from tumors from these samples, such as circulating tumor cells, circulating tumor DNA, or extracellular tumor vesicles (Lone *et al*., 2021).

Proteomic strategies have become necessary in the discovery of biomarkers that could be applied to these samples, for example, in a study that analyzed the proteome of nipple secretion to find a method for early detection of cancer in women. youths. The results in this study identified an average of 1,265 proteins, of which 46 are on the list of 195 proteins under investigation by the Department of Early Detection of the National Cancer Institute of the United States, the interesting part is that 22 of these 46 were found in all samples with cancer and 7 of these 22 were not found in plasma (Shaheed *et al*., 2017). In a study by Chu and colleagues (2019), using body fluids to identify key proteins that might be useful in detecting oral cancer, they collected saliva samples from healthy and sick patients over two years who were subjected to proteomic analysis. Chu et al. identified 24 proteins with the potential to be biomarkers, in addition to some that could be useful for early detection of the disease (Chu *et al*., 2019).

As already mentioned, proteomics is versatile in terms of the samples to be used. An example of the use of a biopsy sample is the study by Madoz and his team, who used biopsies from 15 patients with colorectal carcinoma and used antibody microarrays which allow observing protein expression patterns of tumor cells and compared them with mucosal cells that were not yet affected. The microarray was made up of 224 antibodies specific for proteins of signaling pathways of interest in cancer such as apoptosis, cell cycle, signal transduction, nuclear proteins, and neurobiology, in addition, 8 antibodies were specific for phosphorylations of associated protein kinases (FAK, histone H3, MAPK, etc.). This study identified proteins of interest such as MDM2, CHK1, and ERK, which showed overexpression in patient samples. It is also important to mention the interesting use of microarrays for proteins and how these panels can be made specifically for other types of cancer (Madoz-Gúrpide *et al*., 2007).

5.5 Conclusion

Proteomics is an omic science that has revolutionized cancer studies by expanding existing knowledge, elucidating growth mechanisms and basic biology, and based on this, applying it to the clinical care of patients.

Personalized medicine has been based largely on the study of the proteome, since it allows the identification of biomarkers and therapeutic targets to direct a treatment according to the type of pathology and level of the patient, and in this way minimizing side effects of current chemotherapies. Proteomics allows the study of both patient samples, xenografts or, through the cultivation of immortalized cell lines, the comparative and complementary study in each of these techniques has provided a greater understanding of the mechanisms with which said pathology is addressed, in addition to being able to identify the main function that certain cells have in the behavior of metastasis or resistance to treatment drugs, which has allowed important advances in the adequate treatment of patients, although in some cases the disease is not eradicated, the survival time has presented a significant increase.

The examples of studies shown here have shown how this omics science has highlighted the advantage of using this omics science for the analysis of different pathologies, that although the experimental study is of the utmost importance for the collection of optimal data, each time they have revealed techniques with easier implementation and analysis. In the same way, the use of this omics science was evidenced to translate the knowledge of basic science into the clinic and how its use shows promising and competent data to generate a great impact on public health.

5.6 Acknowledgements

The authors acknowledge the support of CONACYT and CIATEJ.

5.7 Financing

This work has been funded by CF-CONACYT: Paradigmas y Controversias de la Ciencia (project number: 2022-320792).

5.8 References

Albrethsen, J., Angeletti, R. H., Horwitz, S. B., & Yang, C.-P. H. (2014). Proteomics of Cancer Cell Lines Resistant to Microtubule-Stabilizing Agents. *Molecular Cancer Therapeutics*, *13*(1), 260–269. https://doi.org/10.1158/1535-7163.MCT-13-0471

Asami, K. (2014). Epidermal growth factor receptor tyrosine kinase inhibitors for non-small cell lung cancer. *World Journal of Clinical Oncology*, *5*(4), 646. https://doi.org/10.5306/wjco.v5.i4.646

Aslam, B., Basit, M., Nisar, M. A., Khurshid, M., & Rasool, M. H. (2017). Proteomics: Technologies and Their Applications. *Journal of Chromatographic Science*, *55*(2), 182–196. https://doi.org/10.1093/chromsci/bmw167

Buclin, T., Thoma, Y., Widmer, N., André, P., Guidi, M., Csajka, C., & Decosterd, L. A. (2020). *The Steps to Therapeutic Drug Monitoring: A Structured Approach Illustrated With Imatinib*. https://doi.org/10.3389/fphar.2020.00177

Chen, R., Yi, E. C., Donohoe, S., Pan, S., Eng, J., Cooke, K., Crispin, D. A., Lane, Z., Goodlett, D. R., Bronner, M. P., Aebersold, R., & Brentnall, T. A. (2005). Pancreatic Cancer Proteome: The Proteins That Underlie Invasion, Metastasis, and Immunologic Escape. *Gastroenterology*, *129*(4), 1187–1197. https://doi.org/10.1053/j.gastro.2005.08.001

Chu, H.-W., Chang, K.-P., Hsu, C.-W., Chang, I. Y.-F., Liu, H.-P., Chen, Y.-T., & Wu, C.-C. (2019). Identification of Salivary Biomarkers for Oral Cancer Detection with Untargeted and Targeted Quantitative Proteomics Approaches. *Molecular & Cellular Proteomics*, *18*(9), 1796–1806. https://doi.org/10.1074/mcp.RA119.001530

Ciocan-Cartita, C. A., Jurj, A., Buse, M., Gulei, D., Braicu, C., Raduly, L., Cojocneanu, R., Pruteanu, L. L., Iuga, C. A., Coza, O., & Berindan-Neagoe, I. (2019). The Relevance of Mass Spectrometry Analysis for Personalized Medicine through Its Successful Application in Cancer "Omics." *International Journal of Molecular Sciences*, *20*(10), 2576. https://doi.org/10.3390/ijms20102576

Coban, B., Bergonzini, C., Zweemer, A. J. M., & Danen, E. H. J. (2021). Metastasis: crosstalk between tissue mechanics and tumour cell plasticity. *British Journal of Cancer*, *124*(1), 49–57. https://doi.org/10.1038/s41416-020-01150-7

Colnaghi Simionato, A. V. (Ed.). (2021). *Separation Techniques Applied to Omics Sciences* (Vol. 1336). Springer International Publishing. https://doi.org/10.1007/978-3-030-77252-9

Compton, C. (2020). *Cancer: The Enemy from Within*. Springer International Publishing. https://doi.org/10.1007/978-3-030-40651-6

Ding, Z., Wang, N., Ji, N., & Chen, Z.-S. (2021). Proteomics technologies for cancer liquid biopsies Introduction to proteomics in cancer liquid biopsy. *Molecular Cancer*, *21*, 53. https://doi.org/10.1186/s12943-022-01526-8

Farfán, M. J., & Torres, J. P. (2018). Diagnóstico en medicina en la era de las "omicas." *Revista Chilena de Pediatría*, *89*(2), 163–165. https://doi.org/10.4067/S0370-41062018000200163

Feng, Z., Yu, Q., Zhang, T., Tie, W., Li, J., & Zhou, X. (2020). R E V I E W Updates on mechanistic insights and targeting of tumour metastasis metastasis, tumour invasion, tumour microenvironment. *2076 | J Cell Mol Med*, *24*, 2076–2086. https://doi.org/10.1111/jcmm.14931

Ferreira, D., Adega, F., & Chaves, R. (2013). The Importance of Cancer Cell Lines as in vitro Models in Cancer Methylome Analysis and Anticancer Drugs Testing. In *Oncogenomics and Cancer Proteomics - Novel Approaches in Biomarkers Discovery and Therapeutic Targets in Cancer*. InTech. https://doi.org/10.5772/53110

Ferreira, R., Neuparth, M. J., Nogueira-Ferreira, R., Magalhães, S., Aroso, M., António Bovolini, J., Santos, L. L., Oliveira, P., Vitorino, R., & Moreira-Gonçalves, D. (2019). Exercise Training Impacts Cardiac Mitochondrial Proteome Remodeling in Murine Urothelial Carcinoma. *International Journal of Molecular Sciences Article Int. J. Mol. Sci*, *20*, 127. https://doi.org/10.3390/ijms20010127

Gregory, C. D. (Ed.). (2016). *Apoptosis in Cancer Pathogenesis and Anti-cancer Therapy* (Vol. 930). Springer International Publishing. https://doi.org/10.1007/978-3-319-39406-0

Hoi, C., Cheung, Y., & Juan, H.-F. (2017). *Quantitative proteomics in lung cancer*. https://doi.org/10.1186/s12929-017-0343-y

Hulmi, J. J., Penna, F., Pöllänen, N., Nissinen, T. A., Hentilä, J., Euro, L., Lautaoja, J. H., Ballarò, R., Soliymani, R., Baumann, M., Ritvos, O., Pirinen, E., & Lalowski, M. (2020). Muscle NAD+ depletion and Serpina3n as molecular determinants of murine cancer cachexia—the effects of blocking myostatin and activins. *Molecular Metabolism*, *41*, 101046. https://doi.org/10.1016/j.molmet.2020.101046

Jiménez-Morales, S., Hidalgo-Miranda, A., & Ramírez-Bello, J. (2017). Acute lymphoblastic leukemia: a genomic perspective. *Boletín Médico Del Hospital Infantil de México (English Edition)*, *74*(1), 13–26. https://doi.org/10.1016/j.bmhime.2017.11.013

Katsogiannou, M., Boyer, J.-B., Valdeolivas, A., Remy, E., Calzone, L., Audebert, S., Rocchi, P., Camoin, L., & Baudot, A. (2019). Integrative proteomic and phosphoproteomic profiling of prostate cell lines. *PLOS ONE*, *14*(11), e0224148. https://doi.org/10.1371/journal.pone.0224148

Korrodi-Gregório, L., Soto-Cerrato, V., Vitorino, R., Fardilha, M., & Pérez-Tomás, R. (2016). From Proteomic Analysis to Potential Therapeutic Targets: Functional Profile of Two Lung Cancer Cell Lines, A549 and SW900, Widely Studied in Pre-Clinical Research. *PLOS ONE*, *11*(11), e0165973. https://doi.org/10.1371/journal.pone.0165973

Kruse, U., Bantscheff, M., Drewes, G., & Hopf, C. (2008). *Chemical and Pathway Proteomics POWERFUL TOOLS FOR ONCOLOGY DRUG DISCOVERY AND PERSONALIZED HEALTH CARE**. https://doi.org/10.1074/mcp.R800006-MCP200

Kwon, Y. W., Jo, H.-S., Bae, S., Seo, Y., Song, P., & Yoon, S. M. (2021). Application of Proteomics in Cancer: Recent Trends and Approaches for Biomarkers Discovery. *Biomarkers Discovery. Front. Med*, *8*, 747333. https://doi.org/10.3389/fmed.2021.747333

Law, H. C.-H., Lagundžin, D., Clement, E. J., Qiao, F., Wagner, Z. S., Krieger, K. L., Costanzo-Garvey, D., Caffrey, T. C., Grem, J. L., DiMaio, D. J., Grandgenett, P. M., Cook, L. M., Fisher, K. W., Yu, F., Hollingsworth, M. A., & Woods, N. T. (2020). The Proteomic Landscape of Pancreatic Ductal Adenocarcinoma Liver Metastases Identifies Molecular Subtypes and Associations with Clinical Response. *Clinical Cancer Research*, *26*(5), 1065–1076. https://doi.org/10.1158/1078-0432.CCR-19-1496

Le Large, T. Y. S., El Hassouni, B., Funel, N., Kok, B., Piersma, S. R., Pham, T. V., Olive, K. P., Kazemier, G., van Laarhoven, H. W. M., Jimenez, C. R., Bijlsma, M. F., & Giovannetti, E. (2019). Proteomic analysis of gemcitabine-resistant pancreatic cancer cells reveals that microtubule-associated protein 2 upregulation associates with taxane treatment. *Therapeutic Advances in Medical Oncology*, *11*, 175883591984123. https://doi.org/10.1177/1758835919841233

Lin, S., Yin, Y. A., Jiang, X., Sahni, N., & Yi, S. (2016). *Multi-OMICs and Genome Editing Perspectives on Liver Cancer Signaling Networks*. https://doi.org/10.1155/2016/6186281

Lone, S. N., Nisar, S., Masoodi, T., Singh, M., Rizwan, A., Hashem, S., El-Rifai, W., Bedognetti, D., Batra, S. K., Haris, M., Bhat, A. A., & Macha, M. A. (2021). Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments. *Molecular Cancer*. https://doi.org/10.1186/s12943-022-01543-7

Macklin, A., Khan, S., & Kislinger, T. (2020). Recent advances in mass spectrometry based clinical proteomics: applications to cancer research. *Clinical Proteomics*, *17*(1), 17. https://doi.org/10.1186/s12014-020-09283-w

Madoz-Gúrpide, J., Cañamero, M., Sanchez, L., Solano, J., Alfonso, P., & Casal, J. I. (2007). A Proteomics Analysis of Cell Signaling Alterations in Colorectal Cancer. *Molecular & Cellular Proteomics*, *6*(12), 2150–2164. https://doi.org/10.1074/mcp.M700006-MCP200

Mathé, E., Hays, J. L., Stover, D. G., & Chen, J. L. (2018). The Omics Revolution Continues: The Maturation of High-Throughput Biological Data Sources The Continued Promise of Cancer Informatics. *Yearb Med Inform*, 211–233. https://doi.org/10.1055/s-0038-1667085

Mocan, L.-P., Ilieș, M., Melincovici, C. S., Spârchez, M., Crăciun, R., Nenu, I., Horhat, A., Tefas, C., Spârchez, Z., Iuga, C. A., Mocan, T., & Mihu, C. M. (2022). Novel approaches in search for biomarkers of cholangiocarcinoma. *World Journal of Gastroenterology*, *28*(15), 1508–1525. https://doi.org/10.3748/wjg.v28.i15.1508

Monti, C., Zilocchi, M., Colugnat, I., & Alberio, T. (2019). Proteomics turns functional. *Journal of Proteomics*, *198*, 36–44. https://doi.org/10.1016/j.jprot.2018.12.012

Nguyen, N. D., & Wangid, D. (2020). *Multiview learning for understanding functional multiomics*. https://doi.org/10.1371/journal.pcbi.1007677

Ocana, A., & Pandiella, A. (2010). Personalized therapies in the cancer "omics" era. *Molecular Cancer*, *9*(1), 202. https://doi.org/10.1186/1476-4598-9-202

Pan, S., Brentnall, T. A., Kelly, K., & Chen, R. (2013). *Tissue proteomics in pancreatic cancer study: discovery, emerging technologies and challenges*. https://doi.org/10.1002/pmic.201200319

Parisa Karimi, Armin Shahrokni, & Mohammad R Nezami Ranjbar. (2014). *Implementation of Proteomics for Cancer Research: Past, Present, and Future*. https://doi.org/10.7314/APJCP.2014.15.6.2433

Pei, J., Moon, K.-S., Pan, S., Lee, K.-H., Ryu, H.-H., Jung, T.-Y., Kim, I.-Y., Jang, W.-Y., Jung, C.-H., & Jung, S. (2014). Proteomic Analysis between U87MG and U343MG-A Cell Lines: Searching for Candidate Proteins for Glioma Invasion. *Brain Tumor Research and Treatment*, *2*(1), 22. https://doi.org/10.14791/btrt.2014.2.1.22

Qinghong, S., Shen, G., Lina, S., Yueming, Z., Xiaoou, L., Jianlin, W., Chengyan, H., Hongjun, L., & Haifeng, Z. (2015). Comparative proteomics analysis of differential proteins in response to doxorubicin resistance in myelogenous leukemia cell lines. *Proteome Science*, *13*(1), 1. https://doi.org/10.1186/s12953-014-0057-y

Rajesh, S., Cox, M. J., & Runau, F. (2021). Molecular advances in pancreatic cancer: A genomic, proteomic and metabolomic approach. *World Journal of Gastroenterology*, *27*(31), 5171–5180. https://doi.org/10.3748/wjg.v27.i31.5171

Sanh N., Fadul H., Hussein N, Lyn-Cook BD, Hammons G, Ramos-Cardona XE, Mohamed K, & Mohammed SI. (2018). Proteomics Profiling of Pancreatic Cancer and Pancreatitis for Biomarkers Discovery. *Journal of Cell Science & Therapy*, *09*(04). https://doi.org/10.4172/2157-7013.1000287

Shaheed, S.-U., Tait, C., Kyriacou, K., Mullarkey, J., Burrill, W., Patterson, L. H., Linforth, R., Salhab, M., Sutton, C. W., & Sutton, C. (2017). Nipple aspirate fluid-A liquid biopsy for diagnosing breast health. *Proteomics Clin. Appl*, *11*, 1700015. https://doi.org/10.1002/prca.201700015

Shruthi, B., Vinodhkumar, P., & Selvamani, M. (2016). Proteomics: A new perspective for cancer. *Advanced Biomedical Research*, *5*(1), 67. https://doi.org/10.4103/2277-9175.180636

Srinivas, P. R., Srivastava, S., Hanash, S., & Wright, G. L. (2001). Proteomics in Early Detection of Cancer. *Clinical Chemistry*, *47*(10), 1901–1911. https://doi.org/10.1093/clinchem/47.10.1901

van Staveren, W. C. G., Solís, D. Y. W., Hébrant, A., Detours, V., Dumont, J. E., & Maenhaut, C. (2009). Human cancer cell lines: Experimental models for cancer cells in situ? For cancer stem cells? *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, *1795*(2), 92–103. https://doi.org/10.1016/j.bbcan.2008.12.004

Velásquez-Fernández D. (2011). *Genómica y proteómica: Impacto clínico en cáncer* . Cirujano General Vol. 33 Supl. 1 Last Revision July 2022: https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=27653

Zhu, X., Shen, X., Qu, J., Straubinger, R. M., & Jusko, W. J. (2018). Proteomic Analysis of Combined Gemcitabine and Birinapant in Pancreatic Cancer Cells. *Frontiers in Pharmacology*, *9*. https://doi.org/10.3389/fphar.2018.00084