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Proteomics of Extracellular Matrix Components in Fibrotic Diseases

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ABSTRACT

Fibrotic diseases, characterized by excessive deposition of extracellular matrix (ECM) proteins, lead to tissue scarring and organ dysfunction. The ECM plays a crucial role in maintaining tissue architecture and cell signaling. However, during fibrosis, its composition and structure become dysregulated, exacerbating disease progression. Proteomics, the large-scale study of proteins, offers a powerful approach to analyze ECM components and their modifications in fibrotic diseases. This review explores the current state of ECM proteomics in various fibrotic conditions, including cardiac, hepatic, pulmonary, renal, and cutaneous fibrosis. It highlights the potential of proteomics to uncover novel biomarkers, therapeutic targets, and mechanisms underlying fibrotic disease progression. The article also discusses the challenges and future directions in ECM proteomics research, emphasizing the need for advanced technologies and integrative approaches to fully understand ECM dynamics in fibrosis.

Keywords: Extracellular Matrix (ECM), Fibrotic Diseases, Proteomics, Mass Spectrometry, Cardiac Fibrosis.

INTRODUCTION

Proteomics is the large-scale study of proteins, particularly their functions and structures. It is a branch of proteomics that studies the characterizations and functions of the entire proteome of an organism. Fibrotic diseases are chronic wound-healing disorders characterized by tissue and organ fibrosis. They are due to the excessive accumulation of extracellular matrix (ECM) proteins, leading to compromised normal tissue architecture and impaired organ functioning. Proteomics may be defined simply as the large-scale analysis of proteins. It is 'large-scale' in the sense that it aims to analyze as complete a set of proteins as possible in a particular sample, and 'proteomics' is used in the spirit of 'genomics' to describe the analysis of proteins at a global or system-wide level. The study of the proteome can provide a wealth of information not accessible from the complementary genome or transcriptome data. Proteome-aware systems biology approaches have the potential to unravel novel mechanisms of pathogenesis underlying diseases (e.g. host-protein interactions) and to identify new drug targets or molecules amenable to therapeutic intervention [1, 2, 3] Fibrotic diseases are devastating injuries of vital organs such as the heart and kidneys, leading to high rates of morbidity and mortality. Unfortunately, there are no effective therapies to prevent or reverse the fibrotic process. The accumulation of ECM proteins is a common feature of many fibrotic diseases. However, little is known about the composition of the ECMs that form during fibrotic diseases. Many techniques such as biochemical and transcriptomic approaches have been developed to study the ECM. Proteomics platforms, including mass spectrometry, have developed rapidly and have become essential tools in understanding how diseases affect proteins, the activation of cellular signaling pathways, and how post-translational modifications (PTMs) of proteins play a role in making the disease proteome different from the normal proteome. However, in the case of nature diseases, the ECM is poorly characterized due to the biological difficulty of obtaining sufficient material, and little is known about what ECM components are produced or degraded during fibrotic progression. Given the mounting evidence of the relevance of ECM components in fibrotic diseases, it will be important to apply economical proteomic platforms to shed light on ECM modulation during tissue-fibrosis progression [4, 5, 6].

EXTRACELLULAR MATRIX (ECM) COMPOSITION AND FUNCTION

The word "Matrix" means a womb or an interior space. While it is essential to protect and support cell growth, matrices also help control cell behavior. The extracellular matrix (ECM) exists between cells in every tissue of the man. It affects cell metabolism and pathophysiology differently in various biological structures. The ECM is a combination of fibrous and self-assembled macromolecules with hydrophobic and hydrophilic regions. The ECM influences the tissue's viscoelasticity, swelling, and charges. Its macromolecule concentration and osmotic pressure impact mechanical properties, shape, growth rate, and compliance. At the microscopic level, fibrous ECMs are dynamic molecular systems recognized as control centers for tissues. They can control cell proliferation, migration, adhesion, differentiation, apoptosis, and gene expression by altering cell cytoskeletal organization and receptor signaling [7, 5, 8]. Each organ has a distinct ECM which is unique and neatly adapted to its cells. These provide indispensable structures and bioactive attachments for their cells' growth and differentiation. The unique properties of the ECM regulate tissue homeostasis which could prevent invasion, contraction, expansion, and atrophy. Even though this is a deep and important secret for biological structures, it has been poorly understood. It plays a role in cell adhesion and cell interactions, in which coordinated actions by integrated proteins and polysaccharides govern multiple biological activities. The ECM is made up of a cocktail of proteins, proteoglycans, and glycoproteins secreted by the cells. Most of the proteins are the collagens, glycoproteins (e.g., fibronectin), and proteoglycans (e.g., hyaluronan). In the man, many fibrous proteins have been recognized. Collagens are the main fibrous proteins that make up unique fibrous structures with glycoproteins. There are 29 different collagens classified into six classes, each with specific rhythms, structures, and functions. Collagens play an essential role in giving shape during embryonic development, healing, warping tissues, and enhancing or limiting diffusion nutrients of certain tissues. Other than collagens, elastin is considered the second most abundant fibrous protein in man. Elastin constructs stretchy filamentous structures that provide elasticity to organs. One third of the dry weight in the arterial wall is occupied by elastin. Aortas and arteries have a highly branched structure mainly to contain high blood pressure; however, tears or permanent expansion could lead to sudden death. The ECM in the heart is exposed to changes in pressure and volume at each heartbeat, which is also the main cause of heart failure [9, 10, 11].

ROLE OF ECM IN FIBROTIC DISEASES

Focusing on the role of extracellular matrix (ECM) in different fibrotic diseases, starting with cardiac fibrosis. After a brief description of ECM and its components, how remodeling or dysregulation of ECM contributes to the pathogenesis of cardiac fibrosis is discussed. Similarly, ECM-related proteins involved in hepatic, pulmonary, renal, and cutaneous fibrosis including bioinformatics analysis of ECM proteins across different fibrotic organs are explored. How a better understanding of ECM could shed light on the pathophysiology of fibrosis is also addressed. Finally, the effort of proteomics on interpreting ECM-related proteins during different fibrotic disease progression is covered [12, 13, 14]. Dysregulation or degradation of ECM components has been implicated in the development and progression of multiple fibrotic diseases. Fibrotic diseases include the aberrant accumulation of ECM proteins like collagen, fibronectin, and elastin in excess amount in the tissue resulting in the stiffening of the ECM. This excessive stiffer ECM results in the aggravated production of further ECM components. In different fibrotic condition, ECM components play a myriad role in both development and progression of fibrotic diseases. A better understanding of how alterations of ECM regulate the pathological development of fibrosis could enlighten the pathophysiology of diseases [15, 16, 17].

PROTEOMIC TECHNIQUES FOR ECM ANALYSIS

The extracellular matrix (ECM) surrounds all cells in tissues and organs, providing a dynamic structural and biochemical environment. The ECM is composed of diverse proteins, lipids, glycoproteins, glycosaminoglycans and other macromolecules, and has been shown to influence diverse cellular processes including proliferation, differentiation, apoptosis, migration, adhesion, and gene expression [18, 19, 20]. The structures and components of the ECM can vary substantially across tissues, change during development and aging, and be perturbed in disease states. A variety of diseases including fibrosis, atherosclerosis, arthritis and cancer are associated with pathological changes to the ECM. Despite rapidly evolving knowledge with regard to the cellular receptors for ECM components and their intracellular signaling cascades, the role of ectopic ECM components, of ECM perturbations in a non-cell autonomous context, or of how the mechanisms of disease progression might differ from the normal biology seen in adult tissues remain unknown for many ECM-associated diseases [21, 22, 23]. Mass spectrometry (MS)-based proteomics is a powerful biotechnology that can characterize proteins, including their post-translational modifications (PTMs), splicing isoforms and protein-protein interactions, on a large scale

and in a systematic, unbiased manner. Recent advances in mass spectrometry technology have enabled the relative easy acquisition of large amounts of proteomic data. Furthermore, it is now possible and routine to analyze proteomic data independent of the prior characterization of the proteome under consideration. This capability makes proteomics an exciting technology to characterize the ECM [24, 25, 26]. Advances in proteomics technology have facilitated the discovery of a broad range of ECM components in several normal and diseased tissues. This report will provide an introduction and overview of normal and pathogenic ECM components and their known functions. Furthermore, how proteomics technology might be utilized to provide new insights into ECM components, biology and associated diseases will be discussed [27, 28, 29].

CURRENT FINDINGS AND FUTURE DIRECTIONS IN ECM PROTEOMICS RESEARCH

Current state of research and future directions of ECM proteomics, an overview of new findings and advancements. Exciting advancements have been made to further understand ECM components through the lens of proteomics. Proteomic technologies have advanced rapidly and subsequently been applied to complex ECM-associated pathologies with variable degrees of success. An overview of how the field currently stands, current findings, the most recent advancements made, and where proteomic technologies can be used address the uncertainty still surrounding the ECM. In the early 1970s and late 1980s, proteomics was coined as a term describing the study of proteomes (the entire collections of proteins produced by an organism) in their entirety. It wasn't until the late 1990s that it was interpreted as the study of protein expression as a function of time, condition, or environment. With its relative ease of serological protein profiling, proteomics became a go-to approach for discovering disease-associated candidate biomarkers. Initially, there were two approaches to proteomics: hybrid techniques using two-dimensional gel electrophoresis (2DE) and mass spectrometry (MS); and earlier forms of mid-to-high throughput techniques involving methodologies such as enzyme-linked immunosorbent assays (ELISAs), Western blotting, and complement fixation. Suffice to say that both approaches gained traction, but conventional mid- to high-throughput methodologies commonly had questions concerning the detection of novel proteins, while the hybrid techniques suffered from under/over-abundance in terms of proteome coverage and reproducibility issues. Nevertheless, as candidate biomarkers were further studied, it was quickly evident that the plurality of proteins involved needed to be evaluated collectively to better understand their functional relationships. This led to the rise of "deeper" high-throughput activities that utilized more advanced technologies such as array-based ELISA, protein interaction microarrays, and aptamer arrays to monitor many proteins simultaneously in a panel format. Ultimately the technical evolution of proteomics led to increasingly sophisticated experiments that have attempted to include variant proteome characteristics such as post-translational modifications (PTMs), molecular weight (MW) distributions, and isoelectric points (pI) [30].

CONCLUSION

Proteomics has emerged as a vital tool in the study of extracellular matrix components in fibrotic diseases. The application of proteomic techniques, particularly mass spectrometry, has enabled the detailed characterization of ECM proteins and their post-translational modifications, providing new insights into the molecular mechanisms of fibrosis. This review underscores the importance of continuing to develop and apply proteomic technologies to understand the complex interplay between ECM components and fibrotic disease progression. By advancing our knowledge in this area, proteomics holds the potential to identify novel biomarkers and therapeutic targets, ultimately contributing to the development of effective treatments for fibrotic diseases. Future research should focus on overcoming the current challenges in ECM proteomics, including the need for more sensitive and specific techniques, to fully unlock the therapeutic potential of targeting ECM components in fibrosis.

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