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REVIEW ARTICLE

Progression Of Proteomics In Periodontics

Nikkitha. S[1], K. Dhanadivya[2], S.K. Balaji[3]*

[1]*Undergraduate student, Department of Periodontology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India*
[2]*Senior Lecturer, Department of Periodontology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India*
[3]*Professor & Head, Department of Periodontology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India*

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Abstract

Introduction: Proteins are the primary components of cell metabolic pathways. They are responsible for the structural and functional aspects of all living beings. Numerous protein molecules play a indispensable role in the onset, progression, and severity of periodontal disease. Proteomics, the study of expression of proteomes and their functions, has revolutionized dentistry by assisting in the early detection of many disorders through the detection of several biomarkers found in oral secretions. Information from proteins related to the periodontal disease pathogenesis can be used for diagnosis, as means that aids in prevention and supportive treatment. Apart from this, proteomics has the potential to revolutionize the treatment of oral diseases in terms of detecting risk factors, quick diagnosis, prevention, and control, as well as changes the therapeutic philosophy in all areas of dental sciences.

Key words: Proteomics, Periodontal Diseases, Protein Biomarkers

Address for Correspondence:

Dr. K. Dhanadivya,
Senior Lecturer,
Department of Periodontology,
Sri Ramachandra Institute of Higher Education and Research,
Chennai, Tamil Nadu, India
Email: k.dhanadivya@sriramachandra.edu.in

INTRODUCTION

Proteins, the “working power houses “of a cell, play an important part in the metabolic processes of a living organism such as catalysis, structural support and signal transduction.[1] Proteome is the entire set of all proteins in a cell. This includes changes that occur over time and the specific demands and stresses that cells or organisms face. Proteomics is the study of a complete set of proteins expressed by an organism at a particular environment and at a specific stage of the cell cycle.[1]

Periodontitis is an inflammatory disease caused by the interaction of infectious substances with host factors. Periodontium represents a multi-compartment group of interrelating cells and matrices that provide incessant support, proprioception, attachment and physical shield to the tooth.[2] Knowledge of the several proteins involved in the pathogenesis of periodontal disease is useful for the diagnosis, prevention, and management of periodontal disease.

In the field of Periodontology, Proteomes - an organism's protein pool, are vital for understanding periodontal ligament function, regulation, and disease-related protein indicators.[3] Recent advances in proteomic approaches for tissue segregation, protein dissociation, quantification, sequence analysis, and structural interaction hold enormous promise for bringing about changes in periodontal physiology and pathology into the current era. Hence, this article focuses to provide a review about the proteomic approaches applied in the field of periodontology and to compare the proteomes of an organism at different times to identify their actions. The discovery of new protein biomarkers has been a primary driving force in the advancement of proteomic approaches.

TYPES OF PROTEOMICS: Overall proteomics can be divided into three main types such as: Structural Proteomics; Functional Proteomics; Expression Proteomics. Table 1 shows the types of proteomics and its role.

TABLE 1: Types of Proteomics:

STRUCTURAL	FUNCTIONAL	EXPRESSION
Determines the three-dimensional structure and structural complexities of functional proteins.	Studies the protein functions and molecular mechanisms in the cell and determines the protein’s interactions.[4]	Studies the quantitative and qualitative expression of proteins. It can identify proteins specific to disease and novel proteins in signal transduction. Used to study the patterns of protein expression in various cells.

STEPS INVOLVED IN ANALYSIS OF PROTEOMES:

Step 1 - Extraction from the sample: Extraction of proteins from subcellular organelles, followed by purification using centrifugation or chromatography techniques. Insoluble substances are removed by centrifugation, salts by reverse-phase chromatography or protein precipitation prior to the analysis. Complex fractions should be fractioned to obtain sub fractions. The sample is then subjected to Two-Dimensional electrophoresis.[5]

Step 2 – Separation: Two-Dimensional Gel Electrophoresis technique is used for the separation of proteins and is done on the basis of their molecular weight and iso-electric points. This technique allows resolution of thousands of proteins.[5] Other methods like field flow fractionation can also be used, in which the protein separation is based on their mobility.

Step 3 – Identification: A protease excises and digests the isolated protein spots on the gel. Trypsin is the most often used enzyme for protein digestion. Mass spectrometry is used to identify the eluted peptides.[5]

PROTEOMICS IN DENTISTRY

Proteomics is implemented in oral fluid diagnosis, biomarkers identification and to study the bone and enamel structures, especially the dental enamel. Disease detection and oral health surveillance can be done using proteins found in human saliva. The discovery of salivary protein biomarkers begins with the identification of the proteomic composition of the ductal saliva.

Contents of saliva:

- Foreign substances
- Bronchial products
- Bacterial degradation products
- Lipopolysaccharides
- Epithelial and immune cells
- Electrolytes
- Microorganisms
- Serum
- Gingival crevicular fluid

It also contains biomarkers that are specific to physiological features of periodontitis. Proteomics has a wide range of applications in dentistry, and the scope of proteomic technologies are yet to be investigated and explored in dentistry. The analysis of proteins at the molecular level will aid in the evolution of treatment in all dental specialties and will provide insight to the unknown horizons in dental health and disease.

Proteins of the periodontium: The periodontium provides constant support, attachment, proprioception, and physical protection. A total array of expressed proteins will be required to fully comprehend the mechanisms of homeostasis and its response to infection in periodontal tissues. The functions of the proteins present in the periodontium include cell matrix adhesion, signalling, regulating the diffusion of nutrients, waste products and soluble signalling molecules. This protein, along with periodontal ligament, is made up of the intermediate filament network, that plays a role in providing the structural integrity of the periodontium. The lack of cementum markers was an obstacle in determining the molecular mechanism that controls periodontal regeneration and to overcome this, a differently expressed gene was identified, which was termed the cementum protein-23.[6]

PRACTICAL APPLICATION OF PROTEOMICS

Proteomics has a wide range of use in every aspect of science with multiple practical applications. The basis for the discovery of any novel drug is the inactivation of the proteins involved in the disease, by using the 3D structure of the disease related protein. The genetic differences between the individuals are identified, which can be used to develop personalized drugs that can be efficacious for any individual.[6]

PROTEOMIC BIOMARKERS

Periodontitis is a chronic inflammation caused by bacteria. which affects soft and hard support structures that cover the teeth. Traditional methods like radiography cannot diagnose the patients at risk. Evolution in the use of oral fluid as a tool of measuring the current disease condition, has made saliva and other oral fluids the forefront of technology. Although most biomarkers in oral fluid are inflammatory mediators, collagen breakdown molecules that are specific and bone turnover molecules have become a major tool in periodontitis.

Saliva has high potential in monitoring not only general but also oral health and disease. It is a favourable diagnostic tool for screening oral diseases. It is an oral fluid consisting of exocrine components and gingival crevicular fluid. It can be collected without any difficult procedures. Some of the indications for progression of periodontitis are Tumour Necrosis factor, Immunoglobulin (Ig), Matrix Metalloproteinases (MMP 2 and 9), Esterases, Lysozyme, Lactoferrin levels in saliva, Cytokines like C- reactive protein, pentraxin-3, and other interleukins.[6]

Proteomics in gingival crevicular fluid (GCF): GCF was also used to study the biomarkers in healthy individuals and periodontitis patients, which is an inflammatory exudate from the gingival margin. The main component of GCF is composed of soft tissue inflammatory products, some of which are considered a biomarker specific to alveolar bone destruction.[6] The products include, cytoskeleton-related proteins, immune-related protein, circulating blood proteins, enzymes, inflammation-related protein, lipid-related protein. Mass-spectrometry can be used for analysing the components of GCF.

Proteomics and periodontal pathogens: The oral cavity contains numerous microorganisms like bacteria, fungi, protozoa and viruses. Various studies have shown the interactions of these microorganisms with their host in health and disease. Proteomics offers a new perspective to understand these overall changes to which oral microbes adapt to the environmental changes in the mouth. Porphyromonas gingivalis, Treponema denticola, and Aggregatibacter actinomycetemcomitans are few of the microorganisms which are involved in the periodontal pathogenesis.[6]

PROTEOMIC TECHNOLOGIES

A few approaches are obtainable for analytical separation and identification of proteins from complex mixtures.

Two-dimensional gel electrophoresis: Advancements such as the immobilized ph gradient (IPG), that separates proteins by charge in one dimension before separating them by size in the second dimension, have made it possible to reproduce this technique in laboratories. Another important advance is the use of IPG with a single pH unit to improve isolation and intracellular fractionation. Apart from improving sensitivity it determines the localization of proteins in the cell. It is a high-powered technique, but one disadvantage is that the 2D gel electrophoresis has a relatively low throughput to detect small amounts of proteins such as cytokines and signaling molecules.

Mass spectrometry: A mass spectrometer is a very accurate balance for very low mass particles. Protein is usually divided into small fragments (peptides) by the enzyme protease (usually trypsin), and the mass of the peptide is detected by a mass spectrometer. Based on its amino acid sequence, each protein has a distinctive peptide mass fingerprint (PMF), so the peptide mass determined by a mass spectrometer can associate a protein from thousands of proteins in the database. A major advance in mass spectrometry is the capacity of analysers to separate ions (or peptides) and further fragment them into individual amino acids. To reduce sample complexity, the MS approach is often combined with multidimensional liquid chromatography (MDLC) prior to mass spectrometers. This separates the complex protein sample into multiple fractions, and the matched peptides from the two samples co-elute so that the peptides can be compared because they have the same chromatographic properties. The multidimensional protein identification technique is an attractive approach to large-scale analysis of complex samples, allowing more than 1400 proteins to be identified from yeast in a single experiment.[7]

Direct mapping of protein expression in healthy and diseased tissues was achieved in MS analysis of tissue sections. Such analysis reveals variations in protein expression between normal and affected tissues. It can be unique to different tumour types. Schwartz et al. analysed more than 100 glioma patients with a reasonably high throughput.[8] Importantly, the protein patterns described serve as an independent indicator of patient survival, suggesting that this new molecular approach can provide clinically relevant information. Further advancements in the data processing and analytical assessment of imaging MS are beginning to validate the utilization of this technique in clinical practice.[9]

Protein chips: Currently, the main advantage of this technology over conventional protein separation tools is the capacity to analyse protein-protein, protein DNA, or protein RNA interactions, based on the substrate cross-linked to the chip. This technique is important for proteins that are not suitable for 2D gel electrophoresis. Apart from this, the analysis of serum samples is significantly improved using this technique, as the inherent "masking" of serum proteins by the abundant albumin species on 2D gels is significantly reduced.[10]

Tissue microarrays: Over the past century, pathological evaluation of tissue is of paramount importance in the diagnosis of cancer. Improvements in array technology have made it possible to adapt traditional immuno-histochemical detection of protein expression in tissue sections in the high-throughput array format. Through studies it has been evident that the use of immuno-histochemistry of tissue microarray, expressed about 26 selected proteins in more than 1,600 cancer samples from 552 consecutive early-stage breast cancer patients.[11] Hierarchical clustering identified associated clusters of co-expressed proteins and tumour clusters. In this technique, a study group of 368 patients and a validation group of 184 patients were identified. Apart from this a group of 21 proteins whose combined expression significantly correlated with metastasis-free survival has also been reported. Importantly, in multivariate analysis, 21 protein sets were the strongest independent predictors of clinical outcome. [11]

PROTEOMICS IN FUTURE

There are several prospects for future applications of the proteome in the field of diagnosis. Various research activities have been performed to enhance the role of oral and salivary fluids in oral diagnostics. Protein expression and post-translational modification are processes that are dynamic in nature, affecting periodontal tissue. Their identification and quantification alone may not suffice to comprehend their functional changes. Newer techniques are needed to enable a combination of metabolic labeling and identification along with quantification and measurement of synthetic rates.[6] Techniques like Non-Gel based protein separation can be utilized to overcome the constraints of two-dimensional electrophoresis.

CONCLUSION

The composition, behaviour and metabolisms of dental tissues and oral fluids are analysed with the help of proteomics in the last few years.[12] It may revolutionize the management of oral conditions by identifying the etiological factors, help in prompt diagnosis, as well as its prevention and control, which might further change and revolutionize the practice of dentistry. As proteins are the universal component of all functions of living being, the scope of proteomics in health and particularly in the sector of periodontology is predicted to scale greater heights. Therefore, clinical proteomics offers a promise for biomarker discovery with major challenges in the near future.

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